Neural Correlates of Emotion-Cognition Interactions in Healthy Functioning and Adolescent Psychopathology

by

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ABSTRACT

The current dissertation implemented two large studies involving brain imaging and behavioral methods to expand our current understanding of the impact of emotion on cognition. Study one focused on the immediate and long-term impact of emotion on cognition in healthy functioning. Study two focused on identifying alterations in emotional and cognitive processing related to adolescent psychopathology. In Study one, functional magnetic resonance imaging (fMRI) was implemented in conjunction with; (I-i) an attentional capture paradigm containing different levels of emotional and cognitive challenge, (I-ii) the subsequent memory paradigm where memory for stimuli with different levels of emotional challenge from the attentional capture paradigm were examined, and (I-iii) another subsequent memory paradigm where memory for lure items used in the first subsequent memory paradigm were examined. The structure of this study allowed for the investigation of; (I-i) two competing theories of how emotion and attention interact, (I-ii) factors linking the immediate impact of emotional distraction on goal-oriented task performance and its long-term impact on memory, and (I-iii) brain activity linked to different memory operations occurring during the retrieval of emotional memories.

Data were collected on healthy, young adults aged 18 to 35 years. Findings from study one provided novel insights and significant contributions to the cognitive neuroscience of emotion and emotional memory by; (I-i) reconciling two competing theories on the interaction between emotion and attention by taking into consideration the amount of both the emotional and cognitive challenge present, (I-ii) identifying that automatic mechanisms are critical in forming a direct relationship with the immediate impairing and long-term enhancing impact of emotion on cognition, and (I-iii) showing medial temporal lobe activity related to the memory-enhancing

effect of emotion at retrieval could be delineated and linked to disparate memory operations (i.e., encoding and retrieval) that both occur during retrieval.

In study two, a multi-modal imaging approach was implemented to investigate differences in emotional and cognitive processing in adolescents with Axis-I affective-, attentional- and behavioral-based psychiatric disorders. More specifically, in study two changes in the brain associated with adolescent psychopathology were examined by; (II-i) implementing a modified emotional oddball paradigm in conjunction with electroencephalogram recordings and event-related potential (ERP) analyses to assess differences in emotional response and in the emotional modulation of cognition, (II-ii) implementing a modified emotional oddball paradigm in conjunction with fMRI and whole-brain regional as well as network-based analyses to assess differences in executive processes important for response inhibition, and (II-iii) diffusion tensor imaging (DTI) and whole-brain voxel based analyses to assess differences in white matter microstructure.

Data were collected on 20 healthy and 20 clinical adolescents aged 11 to 17 years. Findings from study two provided novel insights and significant contributions to clinical and pediatric neuroscience by; (II-i) providing ERP evidence of increased susceptibility to emotional distraction and emotional modulation of attentional control processes for clinical adolescents, (II-ii) providing fMRI evidence of malfunctional cognitive control and affective networks during goal-oriented processing for clinical adolescents, and (II-iii) providing DTI evidence that differences in white matter microstructure and the developmental trajectory of white matter are part of neuronal sequela associated with adolescent psychopathology.

PREFACE

The research presented as part of study one (Chapters 2-4) in this thesis received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Investigation of brain function using functional neuroimaging tools; the impact of emotion on cognition: investigation of the neural correlates of opposing biases in depression and older adulthood", No. 6912, June 29, 2007. Below, I provide details for the published work included in study one of this thesis and describe the individual contributions of each co-author.

Chapter 2 of this thesis has been published as Shafer, A.T., Matveychuk, D., Penney, T., O'Hare, A.J., Stokes, J., and Dolcos, F. (2012). "Processing of Emotional Distraction is Both Automatic and Modulated by Attention: Evidence from An Event-related fMRI Investigation," Journal of Cognitive Neuroscience, vol. 24, issue 5, 1233-1252. I was responsible for design implementation and piloting, data collection, data analysis, writing the manuscript and manuscript edits. D.M. assisted with design implementation and behavioral piloting. T.P. and J.S. assisted with the development of stimuli. A.J.O assisted with drafting early versions of the manuscript. F.D. conceived the project and as the supervisory author was involved in all stages of this research project.

Chapter 3 of this thesis has been published as Shafer, A.T. and Dolcos, F. (2012). "Neural correlates of opposing effects of emotional distraction on perception and episodic memory: an event-related fMRI investigation," Frontiers in Integrative Neuroscience, vol. 6, article 70, 1-15. This report was based on previously collected data and findings from this dataset were initially reported in Shafer, A.T., Matveychuk, D., Penney, T., O'Hare, A.J., Stokes, J., and Dolcos, F. (2012). "Processing of Emotional Distraction is Both Automatic and Modulated by Attention: Evidence from An Event-related fMRI Investigation," Journal of Cognitive Neuroscience, vol. 24, issue 5, 1233-1252. I was responsible for the data analysis, writing the manuscript and manuscript edits. F.D. was the supervisory author and was involved in all stages of this report.

Chapter 4 of this thesis has been published as Shafer, A.T. and Dolcos, F. (2012). "Dissociating retrieval success from incidental encoding activity during emotional memory retrieval, in the medial temporal lobe," Frontiers in Behavioral Neuroscience, vol. 8, article 177, 1-15. This report was based on previously collected data and findings from this dataset were initially reported in Shafer, A.T., Matveychuk, D., Penney, T., O'Hare, A.J., Stokes, J., and

Dolcos, F. (2012). "Processing of Emotional Distraction is Both Automatic and Modulated by Attention: Evidence from An Event-related fMRI Investigation," Journal of Cognitive Neuroscience, vol. 24, issue 5, 1233-1252; and in Shafer, A.T. and Dolcos, F. (2012). "Neural correlates of opposing effects of emotional distraction on perception and episodic memory: an event-related fMRI investigation," Frontiers in Integrative Neuroscience, vol. 6, article 70, 1-15. I was responsible for the data analysis, writing the manuscript and manuscript edits. F.D. was the supervisory author and was involved in all stages of this report.

The research presented as part of study two (Chapters 5-7) in this thesis received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Non-drug approaches to support mental health in youth: Phase II", No. Pro00009218, March 31, 2010. The research conducted for study two of this thesis forms part of an interdisciplinary research collaboration led by Dr. Sunita Vohra in the Department of Pediatrics at the University of Alberta. Other co-investigators from the University of Alberta included; Dr. Lola Baydala from the Department of Pediatrics; Dr. K. Jessica Van Vliet from the Department of Educational Psychology; Dr. Anthony Singhal from the Department of Psychology; and Dr. Florin Dolcos from the Department of Psychology at University of Illinois Urbana-Champaign. Below, I provide details for the published work included in study two of this thesis and describe the individual contributions of each co-author.

Chapter 5 of this thesis has been published as Singhal, A., Shafer, A.T., Russell, M., Gibson, B., Wang, L., Vohra, S. and Dolcos, F. (2012). "Electrophysiological correlates of fearful and sad distraction on target processing in adolescents with attention deficit-hyperactivity symptoms and affective disorders," Frontiers in Integrative Neuroscience, vol. 6, article 119, 1-13. I was responsible for design implementation and piloting, data collection, data analysis, writing the Methods and Results sections of the manuscript, and edits for the entire manuscript. M.R. assisted with data analysis. B.G. assisted data collection and analysis. L.W. assisted in paradigm development and with manuscript edits. S.V. was responsible for gaining the access to clinical adolescents with Axis-I affective, attentional, and behavioral mental health disorders. A.S. was responsible for writing the Introduction and Discussion sections of the manuscript. F.D., A.S., and S.V. conceived the project. Furthermore, A.S. and F.D. were co-supervisory authors and were involved in all stages of this research project.

DEDICATION

This work is dedicated to my mom Sharon and sister Kate whose unwavering support made its completion a reality. It is also dedicated to my friends who put up with varying periods of what may best be described as mental instability and with long periods of me being absent. Thank you for sticking with me through the rough patches.

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I am truly indebted to my advisor Florin Dolcos whose guidance as had an immeasurable impact on my approach for scientific investigation, and whose patience and perseverance are what surely kept him from giving up on me when I was at times a difficult student to work with. Thank you Florin for teaching me so much and never giving up on me. I am insurmountably grateful for my co-advisor Anthony Singhal whose support and guidance was integral to my completion. Thank you Anthony for always being there to guide and help me through science and life-related challenges. I would like to thank Roger Dixon for serving on my supervisory committee, providing great feedback on many stages this dissertation work, and offering me a new lens by which to view my work. This new lens opened up a new area of research for me and ultimately led to my first post-doctoral position. Lastly, I would like to thank Drs. Christian Bealiua and Wendy Heller for taking the time to be on my dissertation committee; Drs. Jeremy Caplan, Ester Fujiwara, Nikolai Malkhin and the Centre for Neuroscience's Megan Airmet and Carol Ann Johnson for helping me at various points throughout the completion of my doctorate.

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CHAPTER 1

INTRODUCTION

Emotional stimuli tend to capture our attention more easily than non-emotional stimuli, and thus may affect different aspects of our cognition, from lower-level perceptual-based to higher-level executive-based cognitive processes. Investigation of the impact of emotion on cognition is critical for understanding mood and anxiety disorders, in which alterations in emotion-cognition interactions result in heightened awareness of emotional stimuli, uncontrollable intrusive recollection of distressing events, and/or increased emotional distractibility. While considerable advances have been made in understanding the effect of emotion on cognition, open questions still remain regarding their interaction and how it is altered in clinical populations suffering from psychopathology.

Understanding the immediate impact of emotion on perception and attention, and its long-term impact on memory, as well as dissociating cognitive processes involved in emotional memory are among the open questions remaining regarding our understanding of emotion and cognition in healthy populations. Understanding how emotional and cognitive processes are impacted in adolescence due to psychiatric illness, and identification of the neural mechanisms related to maladaptive alterations in these processes are also among the important open questions in the current literature concerning emotion and cognition in clinical adolescent populations.

Therefore, the overarching goals of the present research were to; 1) investigate factors that influence the immediate impact of emotion on attention and perception, assess how these factors influence the long-term impact of emotion on memory, and dissociate different memory operations involved during the retrieval of emotional memories. 2) Investigate factors that influence emotion and cognition interactions in clinical and healthy adolescents. These overarching goals were accomplished using behavioural methods in conjunction with brain imaging tools. Below, I will briefly introduce the brain imaging techniques and behavioral

paradigms used, and discuss in more detail the unresolved issues that were addressed in the present work.

Brain Imaging Methods Employed

Neuroimaging techniques such as magnetic resonance imaging (MRI) and electroencephalography (EEG) have proven invaluable in developing our current understanding of brain-behavior relationships associated with emotion and cognitive processes. Functional information providing details on neuronal populations and networks sub-serving various emotional and cognitive operations can be obtained from functional MRI (fMRI) and event-related potentials (ERPs) that are derived from EEG. These techniques each are complementary (as will be described below) and when used together in multi-modal imaging investigations can offer integrative insights so that a unified theory of neuronal functioning associated with a particular process or disease state can be developed. In addition to functional information, structural information providing details on cortical and subcortical, grey and white matter organization can also be obtained from MRI and diffusion weighted MRI (DW-MRI).

I. Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging is a brain imaging tool used to examine neuronal activity based on the principle of neurovascular coupling. Simply stated, neurovascular coupling is the relationship between neuronal activity (i.e., neuronal firing, action potentials, changes in membrane potential) for an area of neural tissue and changes in blood-flow (i.e., hemodynamic response) in the same area of neural tissue. The blood oxygenated level-dependent (BOLD) response, which is representative of the hemodynamic response, can be measured using fMRI. This is possible due to the different magnetic properties of the hydrogen atom in water molecules when in an environment of oxygenated versus deoxygenated hemoglobin. A detailed report on

MRI physics responsible for generating MR-based (BOLD, DW) images is beyond the scope of the current work, but the basic principles will be briefly mentioned since it is an important tool used in the current work and in cognitive neuroscience in general.

Overall there are two basic concepts behind how MR imaging works. The first concept concerns the properties of atomic nuclei. An atom is the smallest possible amount of a unique element (a unique substance that cannot be further broken down into simpler unique substances). The nucleus of an atom can be comprised of both protons and neutrons. Protons and neutrons inherently possess a property called angular momentum (tendency to rotate in a particular direction and at a particular rate, also known as resonance frequency). In the nucleus, protons and neutrons form pairs that result in a net angular momentum of zero. However, if a nucleus has an uneven number of protons and neutrons (e.g. Hydrogen, with one proton and no neutron), then the angular momentum of that nucleus will be greater than zero and the entire nucleus will possess an angular momentum (also known as spin). This spin results in an electrical current, which when placed in a magnetic field allows for a magnetic moment (a vector describing the amount of torque that is applied to and necessary for an object to be aligned with the field vector of an externally applied magnetic field). Nuclei that possess these properties (i.e., angular momentum and magnetic moment) are considered to be nuclear magnetic resonance (NMR) property nuclei as they are sensitive to manipulation by magnets (Buxton, 2002; Huettel, Song, & McCarthy, 2004).

The second concept behind how MR imaging works concerns how the properties of nuclei behave when placed in a magnetic field. When outside of a magnetic field NMR nuclei have a net magnetization (M) close to zero as the nuclei are randomly oriented and therefore, the magnetic dipoles generated by the electrical currents from the nuclei spins cancel one another

out. However, when placed in a constant magnetic field (B0) the nuclei of hydrogen molecules will align along and rotate about the axis (a.k.a. field vector) of B0 in either a parallel (or low energy state) or antiparallel (or high energy state) manner. The summation of the lower (parallel) and higher (antiparallel) aligned nuclei yields a net dipole moment (M0) in the same direction as B0 as there are far more nuclei aligned in a lower energy state. A small oscillating field [also known as a radiofrequency (RF) pulse or excitation pulse] can then be applied perpendicularly to B0. This RF pulse uses a frequency that is the resonance (a.k.a. natural, Larmor) frequency of the nuclei under investigation and in essence does two things. First, it increases the number of nuclei in the high energy (antiparallel) state. Second, it pushes M0 out of alignment with B0. M0 then differs from B0 in two ways. First, in a longitudinal manner (that is parallel to B0, also known as ML); and second, in a transverse manner (that is perpendicular to B0, also known as MT). The rate at which ML recovers to M0 is called longitudinal relaxation time or spin-lattice relaxation (as nuclei that were forced into a high-energy state go back to their low-energy state) and is denoted as T1. The rate at which MT recovers to M0 is called transverse relaxation time or spin-spin relaxation (as after excitation into the transverse plane the spins of all nuclei are in phase with one another) and is denoted as T2. Transverse relaxation contains information regarding the phase coherence (i.e. the precession the nuclei about the field vector of B0) as after excitation into the transverse plane the nuclei precess about B0 in phase, and phase de-coherence occurs as the nuclei return to their pre-excited state[1]. At the most basic level then, the MR signal is energy that is released by the excited nuclei as they decay (or relax) to their original, pre-RF pulse,

[1] Phase de-coherence of nuclei is the result of intrinsic (interactions amongst each other) and extrinsic (field inhomogeneities) factors. T2* is used to denote the time constant for the rate of decay of the transverse magnetization component that also accounts for local field inhomogeneities. BOLD images are derived from T2*.

states. A process that is called free induction decay. Relaxation rates for the hydrogen in water molecules located in different tissue environments (e.g., oxygenated versus deoxygenated hemoglobin; grey versus white matter) can be assessed and manipulated along either the longitudinal or transverse components of M0 to yield MR images that have been specialized for maximizing a particular contrast of interests (Buxton, 2002; Huettel et al., 2004).

In two- and three-dimensional imaging there are gradient magnetic fields (i.e., phase-encoding gradient and frequency-encoding gradient) that are used in combination with the RF pulse so that each voxel positioned in a two- (x, y) or three-dimensional (x, y, z) array can be tagged with a unique identifier. As a result, the MR signal contains phase and frequency information, and through Fourier Transform this information is translated to the space dimension, thus producing images with varying signal intensities that are used for analysis in cognitive neuroscience research (i.e., examining differences in signal intensities across a series of images associated with corresponding changes in behavioral performance, disease pathology or an interaction between the two).

In the case of fMRI, changes in BOLD response are examined via the different magnetic properties of water in an environment predominated by either oxygenated (diamagnetic) versus de-oxygenated (paramagnetic) hemoglobin. Greater BOLD response in an area is found when more oxygenated hemoglobin is present. Therefore, fMRI is best suited at examining where in the brain things are happening. Although fMRI is a valuable brain imaging technique it is important to note that it is an indirect measure of brain activity. Neuronal activity is electrochemical and, as mentioned above, fMRI examines the vascular response shown to be coupled with this electrochemical activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001).

II. Electroencephalography and *Event-Related Potentials*

Electroencephalography (EEG) is a brain imaging tool based on the principle that continuous and fluctuating electrical currents, generated by populations of neurons, can be measured off the scalp. Voltage measured at the scalp reflects summed excitatory post-synaptic potentials (EPSPs) from pyramidal neurons in the cerebral cortex. Event-related potentials are averages of this electrical activity measured off the scalp that have been time-locked to a specific event. There are two important aspects of ERPs that make them valuable as a brain imaging tool. First, ERPs are directly related to neuronal activity as EPSPs are graded changes in the post-synaptic membrane potential due to the flow of ions (regulated by passive or active channels) across the post-synaptic membrane. Second, ERPs are measured in milliseconds (msec) and therefore offer a much higher temporal resolution for neural markers of information processing compared to fMRI which has a temporal resolution in seconds. A drawback of this brain imaging technique however, is its inability to localize the neural generators underlying the electrical activity measured at the scalp.

An ERP waveform is derived from EEG data that has been processed to remove noise and has been time-locked to and averaged for a stimulus event of interest. Once the ERP waveform is obtained it can be delineated into separate components (i.e., ERP components) based on the onset and duration of deflections and/or inflection points in the waveform. Components are named based on their timing and voltage sign for when their amplitude is the largest (the largest positive value for positively going deflections and the largest negative value for negatively going deflections). For example, a positively going waveform that reaches its peak latency at approximately 100 msec is called a P100 component.

There are four features of an ERP waveform that are used to make inferences about the neural mechanisms of information processing. 1. First is the overall morphology of the waveform. The morphology of the waveform is determined by the number and shape of deflections and inflection points in voltage that occur during a pre-specified time window (a.k.a. epoch). The morphology of a wave form can provide information on the similarity of the cognitive processes engaged during a task. For example, if ERP waveforms for two separate categories of visual stimuli are compared and the waveform has the same morphology for the first half of the epoch but not the latter half, then the neural/cognitive processes associated with the initial mechanisms of stimulus processing are thought to be similar, whereas those associated with later mechanisms are different. 2. Second is the latency of an ERP component. If ERP waveforms generated from two separate stimulus categories possess similar morphology so that the same component is identified, but differences exist in the time to peak for that component, then the neural/cognitive mechanisms associated with processing the two stimulus categories linked to that component are thought to be the same. However, the neural efficiency or access to processing resources is thought to be enhanced for ERP components with faster latencies. 3. Third is the amplitude of an ERP component. If ERP waveforms generated from two separate stimulus categories possess similar morphology but there are differences in amplitude for a specific component, then again (as with latency) it is thought the associated neural/cognitive processes are similar, but the degree to which these processes are engaged or allocated is different. 4. Scalp topography (where over the scalp an ERP waveform was measured) is a fourth source of information that is important when using ERPs. For example, ERP waveforms measured from electrodes placed over the occipital lobe are thought to largely reflect occipital

lobe activity (irrespective of whether potential modulation is 'bottom-up', 'top-down', or some combination of the two).

III. Diffusion Weighted Magnetic Resonance Imaging and the Tensor Model

The same principles mentioned in the section on fMRI are also used to create DW images. The one critical aspect differentiating them is that DW-MRI examines water diffusion based on the principle of Brownian motion rather that the oxygenated-to-deoxygenated hemoglobin ratio fMRI uses. The principle of Brownian motion informs us that unless restricted, the movement of molecules in a suspended liquid will be random. Therefore, the degree of isotropic movement of water molecules in the brain can be used to infer white matter properties as white matter is lipid-based and thus acts as a barrier restricting the random motion of water molecules (water diffusion in healthy white matter is anisotropic). DW-MRI generates maps of an apparent diffusion coefficient (ADC), analogous to the BOLD maps generated by fMRI.

Unlike in fMRI, where the rises and declines in the BOLD signal can be directly examined (with the exception of fast event-related designs), the tensor model is applied is to the raw ADC maps to provide more information about diffusion. The tensor model uses 6 parameters (three eigenvalues and three eigenvectors) to explain water diffusion within a given space (e.g., voxel). The three eigenvalues quantify directionality in 3-dimensional space and eigenvectors quantify magnitude. These tensor parameters can then be singled out or combined (as described below) to create diffusivity parameters, the interpretation of which informs us about the tissue microstructure that produced them. The first eigenvalue ($\lambda 1$) represents the direction where diffusion is the greatest within a voxel (i.e., parallel with the direction of white matter fiber tracts). This eigenvalue is also known as axial diffusivity (AD) as it is follows the main white matter axis in the voxel. The second and third eigenvalues represent diffusion

perpendicular to the main white matter axis in the voxel. These two values are collapsed into one measure for perpendicular diffusion by taking their average. This value is known has radial diffusivity (RD). The average of all three eigenvalues is called mean diffusivity (MD) and represents general diffusivity within a voxel regardless of directionality. All three of these tensor parameters can be used to calculate an index that measures the overall anisotropic diffusion of the tensor (i.e., fractional anisotropy, FA).

There are two important aspects of FA to consider. First, FA offers a simple way of comparing the overall anisotropy of an area of tissue as it ranges from 0-isotropic to 1-anisotropic. Second, although FA offers a good index of overall anisotropy it is sensitive to many tissue characteristics that result in changes in anisotropy (e.g., the degree of myelination, fiber coherence, fiber density, axon diameter, tract geometry, presence of crossing fibers). As a result, it can be misleading to make inferences about the underlying tissue microstructure when interpreting FA alone. Thus, interpreting FA in the context of other diffusivity parameters (AD, MD and RD) allows for more informed inferences to be made about the characteristics of the tissue microstructure. However, the tensor model is limited and parallels between actual white matter integrity can only be made with the help of animal work verifying the relationship between physical changes in white matter microstructure and diffusion parameters as determined by the tensor model.

Behavioral Methods Employed

I. The Attentional Capture 'Paradigm'

Attentional capture is the phenomenon (Lavie & Fockert, 2006; Ruz & Lupianez, 2002) by which a salient, exogenous stimulus automatically captures and reorients attention for continued processing. Attentional capture 'paradigms' are when the attentional capture

phenomenon is tested in the context of another paradigm. Attentional capture 'paradigms' are typically used to determine either the automaticity with which a stimulus is processed (e.g., stimuli with emotional vs. neutral properties) or the degree of modulation conceded by an ongoing cognitive process. For example, the visual search paradigm is implemented with the attentional capture phenomenon to examine automaticity and cognitive modulation. Concerning the former, pop-out visual search is an example of an attentional capture 'paradigm'. Concerning the latter, a salient exogenous distracter stimulus presented simultaneously with a target stimulus during a goal-oriented cognitive task is another example of attentional capture 'paradigm' (e.g., a salient distracter presented during a more difficult feature-based visual search). Although, these two facets of information processing investigated by attentional capture 'paradigms' may in many cases may be linked. For example, the amount of automaticity for a stimulus may be related to number of ongoing cognitive processes, and/or the degree of modulation experienced by an ongoing cognitive process may depend on the automaticity by which the distracter stimuli can be processed.

Currently, attentional capture 'paradigms' are commonly used to investigate the degree of modulation of an ongoing cognitive process. This is largely due to the generation and instantiaion of the *load theory of selective attention* (Lavie, Hirst, de Fockert, & Viding, 2004; Lavie & Tsal, 1994). According to the load theory of selective attention, distractors have a differential impact on task-relevant processing depending on the "processing load" and requirements of the main task. Specifically, it has been proposed that whereas high load on executive-based cognitive processes (e.g. WM) increase processing of task-irrelevant distraction, high load on perceptual-based processes (e.g. orientation discrimination) eliminates distractor processing. Processing load at the perceptual-based level as defined by Lavie (2005) represents

the degree of perceptual processing requirements necessary for successful perceptual identification. For example, the perceptual load for a task is said to increase when the number of items in a display increases or when the attentional demands necessary for identification of the same number of items increase (i.e. – variations in color or contrast make it more difficult to identify a set number of items).

Research investigating the automaticity of emotion and factors that influence the interaction between emotion and attention during lower-level perceptual-based tasks have largely been examined implementing this paradigm (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Vuilleumier, Armony, Driver, & Dolan, 2001). Investigation of *Issue I* in study one of the present work implemented an attentional capture paradigm such that salient, exogenous stimuli were presented during a perceptual-based orientation discrimination task. This task had varying degrees of perceptual load and the salient, exogenous stimuli (i.e., distracters) had varying degrees of emotional content. Therefore, it was possible to examine the impact of cognitive challenge and emotional charge on the automaticity of emotion processing.

II. The Subsequent Memory Paradigm

The subsequent memory paradigm (Paller, Kutas, & Mayes, 1987) has been used to examine changes in neural activity (as measured by EEG and fMRI) associated with differences in memory performance (i.e., remembered vs. forgotten). Neural activity linked to successful memory can be identified during either encoding or retrieval. In this paradigm participants first complete a study phase where they are shown (typically one a time) a number of to-be-remembered stimuli. In recognition-based subsequent memory paradigms, the stimuli are again shown (typically one at a time) after a delay period (a.k.a. retention interval) in a 'test' phase. Participants then indicate with a button press whether a particular stimulus is 'old', was

previously seen or 'new', was never seen before. Recognition memory paradigms may allude to mechanisms associated with recall memory by incorporating confidence ratings after each stimulus is shown during the 'test' phase. The basis for this assumes the strength of the memory signal or trace is graded depending on whether it can be retrieved freely without any memory cues (and therefore has a very strong signal/trace) to whether it can't be retrieved at all even in the presence of cues or the item itself (a very weak signal/trace). Brain activity for forgotten items is then averaged and subtracted from activity for remembered items (remembered – forgotten). The resultant activity is the difference due to memory (Dm effect) and is interpreted to be activity important for memory formation (if brain activity is recorded during encoding) or retrieval (if brain activity is recorded during retrieval).

The impact of emotion on memory can be examined via the subsequent memory paradigm by calculating and then comparing two Dm effects [one for neutral items and one for emotional items (Dolcos & Cabeza, 2002; Dolcos, LaBar, & Cabeza, 2004b)]. That is, the Dm effect for neutral memory [Neutral Dm, (Neutral Remembered – Neutral Forgotten)] is then compared to the Dm effect for emotional memory [Emotional Dm, (Emotional Remembered – Emotional Forgotten]. Brain areas (as shown via fMRI) or ERP components (as revealed using EEG) showing significant differences between Emotional Dm and Neutral Dm identify where and when (respectively) emotional modulation of memory processes occur. This paradigm can be further expanded adding additional variables that may influence emotion's impact on memory by either enhancing memory for emotional relative to neutral items or by impairing emotional memory (e.g., full versus divided attention during encoding). Investigation of *Issues II* and *III* in study one of the present work implemented the subsequent memory paradigm to examine the

impact of emotion on encoding and retrieval for immediate recognition memory, and encoding for delayed recognition memory.

III. The Modified Emotional Oddball Paradigm

The modified emotional oddball paradigm is a derivative of the original emotional oddball paradigm. In the original emotional oddball paradigm (Cacioppo, Crites, Bernston, & Coles, 1993; Crites, Cacioppo, Gardner, & Bernston, 1995; Ito, Larsen, Smith, & Cacioppo, 1998) a stream of images is presented one after the other. Most of these images are of one stimulus type, called 'standard' images, and are typically meaningless and carry very little to no affective information. Another stimulus type [normally containing images that differ along one dimension (e.g., emotional and neutral images)] is presented with less frequency than the standard images. These images are called 'oddball' images. Participants are instructed to make a button press anytime they see an oddball image. This paradigm allows one to examine the interaction between 'bottom-up' attention and emotion. That is, when both emotional and non-emotional images are oddball items only differing in their emotional properties, then differences in performance/brain activity will result due to differences in the deployment and/or allocation of cognitive resources. Behaviorally, reaction time (RT) is slower when responding to an emotional relative to non-emotional oddball stimulus and this difference is thought to reflect increased processing of the emotional images. Brain activity (fMRI or EEG) can be recorded while this task is performed. Paralleling behavioral findings, brain imaging data show emotional oddballs receive increased resources relative to non-emotional, neutral oddballs.

This original paradigm was altered in order to examine 'top-down' attention-emotion interactions in addition to 'bottom-up' interactions. In the modified emotional oddball paradigm an extra oddball category (non-emotional targets) was added (Fichtenholtz et al., 2004; Wang,

McCarthy, Song, & Labar, 2005). Participants were now instructed to look for and respond to the target oddball images in the picture stream. However, the other emotional and neutral oddballs remained in the task and are now referred to as distracter oddballs. Controlling for the number of frequent images in between the presentation of a distracter and target oddball enables the target oddballs to be grouped according to the type of preceding distracter oddball. Target oddballs could then be considered Targets-after-Emotional or Targets-after-Neutral. As a result, the modified emotional oddball paradigm allows for examination of the interaction between the dorsal (attentional control) network engaged by the presence of a non-emotional target oddball, and the ventral (emotion) network engaged by the presence of an emotional distracter oddball. Furthermore, general emotional and goal-oriented attentional processing can be examined by assessing the response to emotional versus neutral distracter oddballs and the response to target versus distracter oddballs. This paradigm has proven successful at identifying brain regions important for goal-oriented attentional control that are also susceptible to modulation by emotional distraction (Wang, Krishnan, et al., 2008; Wang, LaBar, et al., 2008).

In addition to adding another oddball category, response criteria and options can also be modified. Rather than responding to only target oddballs, participants can also be instructed to make one response to all stimuli that are not targets and another, separate response to target stimuli. Changing the response options this way creates a common, prepotent response that must be inhibited whenever a target oddball is presented. Response inhibition in conjunction with goal-oriented processing now play an important part in successful task performance. This modification is especially suitable for use in populations where impulse control and executive attention deficits are observed. Investigation of *Issues IV* and *V* in study two of the present work utilized the modified emotional oddball paradigm to examine emotion, attention and response

inhibition processes in healthy adolescents and in clinical adolescents with affective, attentional, and behavioral psychiatric disorders.

Issues Investigated

STUDY ONE: An fMRI Investigation of the Immediate and Delayed Impact of Emotional Distraction in a Sample of Healthy Young Adults.

Issue I. The Impact of Emotional Distraction on Perception: The Role of Attentional Load and Emotional Charge.

Extant research shows emotional items typically capture and engage more processing resources compared to non-emotional items. However, whether or not this initial capture of resources depends on the presence of attention or can occur automatically (independently of attention) is a matter of debate (Pessoa et al., 2002; Vuilleumier et al., 2001). Previous investigations examining the interaction between emotion and attention show support for either one of two main competing views. The traditional view (Vuilleumier et al., 2001) posits that emotion, especially that which conveys threatening information, presumably due to its biological relevance for ensuring survival is given priority and can therefore occur automatically (or independent of attentional constraints). A more recent competing view (Pessoa et al., 2002) suggest emotion is not privileged and as with all other types of stimuli requires attentional resources to be processed. While both views have provided compelling evidence supporting one and refuting the other, both views have failed to properly control for the two manipulations that are crucial to understanding how emotion and attention interaction (i.e., availability of attention and the degree of emotion). Studies that provide support for the traditional view do not control for the degree of attentional engagement and studies that provide support for the competing view, while parametrically manipulating attention, do not control for the degree of emotion used.

Therefore, the primary research goal for *Issue I* was to investigate the traditional and competing views of emotion and attention when controlling for both the degree of emotional content and the availability of free attentional resources. Furthermore, we were interested in identifying brain regions associated with the detrimental impact of versus reduction in the effect of emotional distraction on behavior. Thus, the secondary research goal for *Issue I* was to dissociate neural responses reflecting the negative impact from those reflecting the ability to minimize or eliminate the negative impact of emotional distraction on behavior.

Issue II. The Impact of Emotional Distraction on Memory: Linking the Immediate and Delayed Influence of Emotional Distraction on Cognition.

One key factor to understanding maladaptive alterations in information processing (i.e., enhanced awareness of and/or memory for negative events) observed in affective mental health disorders (e.g., anxiety and depression) is knowledge of how the neural mechanisms associated with the initial impact of a negative event relate to those associated with later memory for that event. Consequently, an open question in the emotion literature concerns the relationship between the immediate impact of emotional distraction on perception and the long-term impact on memory. Previous research on emotional distraction has identified two mechanisms by which it occurs, either an automatic [amygdala (AMY) based] and/or attention-mediated [prefrontal cortex (PFC) and temporal occipital cortex (TOC) based] mechanism (Morris, Ohman, & Dolan, 1999; Vuilleumier et al., 2001). Interestingly, previous investigations of emotional memory also shows two routes responsible for the memory enhancing effect of emotion, either an automatic [AMY-hippocampus (HC) based] and/or attention-mediated (PFC based) route (Dolcos, LaBar, & Cabeza, 2004a; Dolcos et al., 2004b; Kensinger & Corkin, 2004).

While these two separate lines of research point to neural correlates associated with automatic and attention-mediate mechanisms of emotional distraction and memory, the relationship between the engagement of either of these mechanisms early (i.e., during perceptual-based processes) versus late (i.e., during memory-based processes) in the information processing stream remains unknown. Data from behavioral investigations of how the allocation of resources during perception influence subsequent memory for task-irrelevant items presented during the perception task, shows reducing resources for task-irrelevant non-emotional items during perception reduces subsequent memory for those items (Uncapher & Rugg, 2005, 2008). Whereas, the effect of dividing resources for task-irrelevant emotional items at perception has less of an effect on subsequent memory performance; this diminished effect is largely thought to occur due to the increased processing (as evidenced by increased distraction) the task-irrelevant emotional items receive relative to the neutral items (Kensinger & Corkin, 2003; Reber, Perrig, Flammer, & Walther, 1994). These data suggests that attention-mediated mechanisms play an important role in the relationship between processes involved in the immediate (impairing) effect of emotion on perception and the long-term (enhancing) effect of emotion on memory, however, the exact circumstances in which a direct (e.g., enhanced distraction and memory) or indirect (e.g., enhanced emotional distraction and decreased memory) relationship exists remain unknown. Furthermore, the associated neural correlates of this relationship remain unclear.

Therefore, the overarching goal of *Issue II* was to investigate the circumstances in which a direct relationship between emotional distraction and memory is evident, and to identify shared and unique neural correlates of these processes that may promote/facilitate a direct relationship.

Issue III. The Long-Term Impact of Emotion on Cognition: Dissociating Memory Processes Involved in the Memory-Enhancing Effect of Emotion.

Emotion enhances item-based memory (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003). This enhancement is associated with increased engagement of emotion (amygdala - AMY) and memory (hippocampus – HC and parahippocampus, PHC) related medial temporal lobe (MTL) regions during both encoding and retrieval (Dolcos et al., 2004b; Dolcos, LaBar, & Cabeza, 2005; Kensinger & Schacter, 2005; McGaugh, 2004). One unclear aspect related to the cognitive neuroscience of memory concerns the dissociation between brain activity linked to process involved in retrieval success from that linked with processes involved in encoding during retrieval (Stark & Okado, 2003). Due to the nature of recognition memory tasks used to study the neural correlates of memory retrieval, it is unclear whether MTL regions identified as being associated with retrieval processes are unique to retrieval or are common to both the successful retrieval of previously encoded items and incidental encoding processes that occur during retrieval.

Investigations of MTL activity associated with incidental memory formation during non-emotional memory retrieval found MTL regions associated with neutral retrieval success largely overlapped with those involved in the incidental encoding success of lure items (Stark & Okado, 2003). Even though a large amount of overlap was found, specificity within the HC was identified such that HC areas were associated with retrieval after accounting for activity related to incidental encoding during retrieval. However, to our knowledge this issue remains unexplored for emotional memory retrieval. Therefore, it is unclear whether or not activity linked to the memory-enhancing effect of emotion identified in MTL-based emotion and memory regions during emotional memory retrieval can be distinguished from activity related to the memory-enhancing effect of emotion associated with the incidental formation of emotional memories during retrieval.

Thus, the main goal in *Issue III* of study one was to distinguish between memory processes involved in the memory-enhancing effect of emotion. This was investigated by using fMRI in conjunction with an experimental design that allowed for the dissociation of MTL involvement in retrieval success from MTL involvement in incidental encoding success that occurred during the retrieval task.

STUDY TWO: A Multi-modal Imaging Investigation of Functional and Structural Alternations Associated with Adolescent Psychopathology.

Issue IV. The Impact of Emotional Distraction on Goal-Oriented Target Processing in Adolescent Psychopathology - ERP Evidence

In situations where one's survival is not in immediate danger, attentional capture by emotional stimuli may result in distraction from task- or goal-oriented behaviour. Consequently, the ability to inhibit emotional distraction is crucial to successful goal-relevant behaviour. As with certain psychiatric illnesses studied in adults, an ability to inhibit emotional distraction may be also be impaired in adolescents with psychopathology. Emotion processing and attentional control are sub-served by two separate, but integrated networks (Iordan, Dolcos, & Dolcos, 2013; Yamasaki, LaBar, & McCarthy, 2002). The emotion network typically includes ventral neural structures and is associated with two event-related potential (ERP) markers; an early posterior negativity (reflecting increased allocation of attentional resources) and late posterior positivity (LPP, reflecting continued cognitive resource allocation to motivationally relevant or high arousal items). The attentional control network (ACN) involves more dorsal neural structures and is also associated with two ERP markers; an early frontal negativity (reflecting cognitive control) and mid-latency parietal positivity (index of executive attention). The ACN network is active when engaged in goal-relevant processing, but also in the inhibition of

emotional distraction. While previous research examining spatial correlates of emotion-attention interactions in adults with major depressive disorder showed reduced ability to inhibit emotional distraction due to dysfunction in the ACN (Wang, LaBar, et al., 2008), the impact of emotional distraction on cognitive control in clinical adolescent populations remain less clear.

Hence, the primary research goal in *Issue IV* was the identification of alterations in ERP markers of emotion-attention interactions in adolescents with affective, attentional, and behavioral psychiatric disorders.

***Issue V.* Neural Correlates of Impaired Response Inhibition in Adolescent Psychopathology – fMRI Evidence**

Adolescence is a time period where increases in risky behaviors are evident as cognitive control procesess are undergoing protracted maturation (Casey, Getz, & Galvan, 2008; Casey, Jones, & Hare, 2008). Characterizing impulse control deficits associated with risk-taking behaviors is impaired (i.e. reduced) response inhibition (Luna & Sweeney, 2004). These problems are exacerbated in many clinical adolescent populations where risky behaviors are more prevalent and response inhibition is further reduced. Brain mechanisms associated with the more extreme impairment in response inhibition that is observed in adolescent psychopathology remains unclear. However, it is an important topic for study as increased risky behavior in adolescent psychopathology, coupled with psychiatric disorders as a leading factor for suicide place these individuals at the greatest risk for adolescent mortality. Research exploring the neural mechanisms of response inhibition in specific adolescent psychiatric illnesses have yielded both consistent and inconsistent findings. While PFC involvement is known (Deveney et al., 2012; Diler et al., 2014; Diler et al., 2013), specificity concerning its involvement is lacking with reports showing altered involvement in response inhibition for a number of differing sub-regions.

In addition to PFC involvement, hyperactive ventral frontal-striatal circuitry during response inhibition has been associated with increased reward sensitivity in healthy adolescents (Somerville, Hare, & Casey, 2011). However, changes in network behavior linked to response inhibition remains largely unexplored in clinical adolescent populations.

Therefore, the primary research goal for *Issue V* was to identify regional and network alterations associated with increased impairment in response inhibition observed in adolescent psychopathology.

Issue VI. Alterations in White Matter Microstructure Associated with Adolescent Psychopathology – DTI Evidence

Findings from research presented in this document emerging from the investigation of *Issues IV* and *V* showed changes in brain function linked to impairments in behavioral function between clinical and non-clinical adolescents. Moving from functional differences to an examination of structural (e.g., white matter) differences that exist between these groups will provide a more comprehensive picture of the neuronal changes associated with adolescent psychopathology. Although a number of studies in the last decade have begun to shed light on white matter changes related to brain maturation during adolescence (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008), alterations in white matter during adolescence due to psychopathology remain largely unknown. Research on microstructural white matter abnormalities in clinical adolescents is limited and the findings are somewhat conflicting, but the majority of studies show decreases in FA compared to non-clinical, control adolescents. Although some studies show opposite findings and report increases in FA. Consequently, alternations in white matter microstructure in adolescence due to psychopathology remain unclear. Furthermore, since both ERP and fMRI techniques provided evidence of alterations in

emotion and attentional processing in clinical compared to healthy adolescents, we sought to further examine structural alterations between groups that may be associated with the observed functional differences. Thus, the primary research goal for *Issue VI* was to investigate differences in the white matter microstructure between clinical and non-clinical adolescents.

Thesis Overview

The goal of the present work was to investigate open questions on the subject of the interplay between emotion and cognition in healthy and clinical groups. More specifically, these questions focused on (1) the immediate and delayed impact of emotional distraction on cognition, and (2) alterations in the neural correlates of emotion and cognition in clinical compared to non-clinical adolescents. Two large studies using behavioral and brain imaging methods were employed to address these questions. Study one used fMRI in conjunction with the attentional capture and subsequent memory paradigms to investigate the immediate and delayed impact of emotional distraction on cognition. Study two used ERP and fMRI in conjunction with the modified emotional oddball paradigm as well as DTI to investigate functional and structural alterations in adolescent psychopathology. The empirical work presented in the following thesis is divided into 6 chapters (2-7). Each chapter corresponds to an issue outlined in the 'Issues Investigated' section above. The last chapter, Chapter 8, summarizes the key findings from Chapters 2 through 7 and discusses their significance. Chapters 2-5 are published and their contents were kept identical to the published versions, with the exception of minor formatting changes for dissertation publication, in accordance with the Faculty of Graduate Studies and Research's requirements. Chapters 6 and 7 are currently "in submission", being prepared for peer-review evaluation and publication.

CHAPTER 2

THE IMPACT OF EMOTIONAL DISTRACTION ON PERCEPTION: THE ROLE OF ATTENTIONAL LOAD AND EMOTIONAL CHARGE

Processing of Emotional Distraction is both Automatic and Modulated by Attention: Evidence from an Event-Related fMRI Investigation

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Possibly because of their relevance for survival, emotional stimuli can affect how we perceive our environment. For instance, emotion can enhance detection by altering the contrast sensitivity required for non-emotional items to enter awareness (Phelps, Ling, & Carrasco, 2006), and can increase or decrease visual estimates of the surrounding environment (Schnall, Harber, Stefanucci, & Proffitt, 2008; Stefanucci & Proffitt, 2009; Stefanucci, Proffitt, Clore, & Parekh, 2008; Stefanucci & Storbeck, 2009; Teachman, Stefanucci, Clerkin, Cody, & Proffitt, 2008). Although it is generally accepted that emotional items can capture attention, whether their processing is automatic or depends on available attentional resources is a matter of current debate (Pessoa, 2005; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Vuilleumier, 2005; Vuilleumier, Armony, Driver, & Dolan, 2001). A limitation of previous investigations is that they have not systematically assessed the impact of emotional charge of task-irrelevant distraction in conjunction with manipulations of the attentional demands of the main cognitive tasks. Here, we used functional magnetic resonance imaging (fMRI) to investigate the effects of attentional and emotional charge manipulations in a perceptual task on processing task-irrelevant emotional distraction, and to identify the neural circuitry underlying the impairing impact of emotional distraction on perceptual processing and the neural correlates of minimizing the impact of such distraction. Investigation of these issues in healthy participants has implications for understanding maladaptive emotion-cognition interactions occurring in affective disorders.

The Debate: The Traditional vs .Competing Views of Emotion and Attention

Currently, the emotion literature presents two main competing views on how emotion and selective attention interact with each other: a traditional view (Vuilleumier et al., 2001) and a competing view (Pessoa, McKenna et al., 2002). The traditional view proposes that processing of emotional information, especially threatening (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003), is given priority and hence it occurs automatically and is not limited by the availability of attentional resources (Morris, Ohman, & Dolan, 1999). In contrast, the competing view (Pessoa, McKenna et al., 2002; Pessoa, Padmala, & Morland, 2005), based on Desimone & Duncan's (1995) biased competition model of selective attention, proposes that processing of emotional stimuli requires attentional resources. Thus, according to this view, emotional stimuli compete for neural representation with all stimuli, and hence suggest a top-down regulation of emotion processing.

Evidence supporting the largely accepted and intuitive view that emotional information is processed automatically shows that emotional stimuli can be detected and processed with increased efficacy, and that this privileged processing depends on the amygdala (AMY), a main brain structure associated with emotion processing. For instance, using visual search paradigms, a series of behavioral studies found rapid and accurate detection of schematically depicted threatening faces, presented in a display involving similar distractors. This effect is so-called "face in the crowd", "snake in the grass", or "pop-out" effect (e.g., Hansen & Hansen, 1988; Ohman, Lundqvist, & Esteves, 2001). Also, evidence from AMY patients shows that intact AMY is needed to observe enhancement of attention by emotional stimuli, which eliminate "attentional blinks" during processing of rapidly succeeding stimuli (Anderson & Phelps, 2001). Further supporting the traditional view and the role of the AMY, brain imaging evidence shows that facial stimuli with emotional expressions (e.g., expressing fear) can be processed even in the

absence of awareness (Whalen, Rauch et al., 1998). This and other evidence led to the generally accepted notion that processing of emotional information occurs automatically (i.e. efficiently), and does not depend on available attentional resources (Hansen & Hansen, 1988; LeDoux, 1996; Moors & De Houwer, 2001; Morris et al., 1996; Morris et al., 1999; Ohman, Flykt, & Esteves, 2001; Vuilleumier et al., 2001). It is important to note that only relatively recently has the operational definition of automaticity become a primary concern when investigating the automatic nature of cognitive processes. Previously, an exact definition of automaticity was muddled by its role in the cognitive process being investigated (e.g., perception, learning, emotion) and by its many separate but related constituting features (e.g., efficiency, intentionality, controllability, awareness). It is now recognized that the features of automaticity need to be separately examined in order to have a better understanding of the process under investigation (see Moors & De Houwer, 2006 for a comprehensive review). Here we specifically focus on the efficiency (attentional demand) aspect of automaticity.

Strong brain imaging support for the traditional view comes from an influential fMRI study by Vuilleumier and colleagues (Vuilleumier et al., 2001). In this study, attention was manipulated by asking subjects to attend either to pairs of houses or faces, which were presented in a four-picture display around a fixation point. The pictures in the house-pairs were either identical or different, whereas the faces were either fearful or neutral, and the subjects were asked to attend either to houses or faces and to make same/different judgments. Supporting the view that emotion processing occurs automatically and independently of the attentional focus, fMRI results revealed increased AMY activity to the fearful faces regardless of whether they were attended or not. Also consistent with the traditional view, response times to houses were slower when fearful faces were displayed as distractors.

Although the exact mechanisms that allow for automatic processing of emotional information are not fully understood, extant evidence points to the existence of direct sub-cortical pathways that reach the AMY independently of the typical cortical connections subserving various sensorial modalities (Vuilleumier, 2005). This is consistent with the evidence that emotional stimuli can also benefit from enhanced processing due to their ability to "capture attention" and re-allocate processing resources (Adolphs, 2004; Anderson & Phelps, 2001; LeDoux, 2000; Pourtois, Grandjean, Sander, & Vuilleumier, 2004; Pourtois, Schwartz, Seghier, Lazeyras, & Vuilleumier, 2006; Price, 2003; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). As a result of this "parallel processing" that allows for both automatic, non-conscious, pre-attentional processing and enhanced conscious processing boosted by the engagement of attentional mechanisms, emotional stimuli are processed with increased efficacy.

There are also open questions regarding the validity and generalizability of the traditional view. For instance, although animal studies provided direct evidence for the existence of the above mentioned sub-cortical route (LeDoux, 2000), human lesion (Anderson & Phelps, 2001) and neuroimaging (Morris et al., 1999) research has provided only indirect evidence that such a pathway exists in humans. Also, even if the proposed sub-cortical route exists in humans, executive control attentional systems have shown top-down attention effects as early as the lateral geniculate nucleus of the thalamus (O'Connor, Fukui, Pinsk, & Kastner, 2002), suggesting that attention could still act on this suggested sub-cortical route.

Representative brain imaging evidence supporting the competing view comes from work by Pessoa et al. (Pessoa, McKenna et al., 2002), which challenged Vuilleumier et al.'s findings and hence triggered an interesting debate concerning the role of attention in early emotion processing (compare Pessoa, McKenna et al., 2002; Vuilleumier et al., 2001). The main

methodological criticism raised by Pessoa et al. (Pessoa, McKenna et al., 2002) was that previous studies failed to reveal evidence for modulation of emotion processing by attention because the tasks used were not demanding enough to reduce the availability of processing resources to be engaged by emotional information – hence, the findings supporting the automaticity of emotion processing. To address this limitation, Pessoa et al. (2002) devised a more difficult task, in which subjects had to fixate on centrally displayed faces (males or females, with fearful or neutral expressions) and either make a gender judgment or specify if two peripherally displayed bars were oriented in the same direction or not. Thus, similar to Vuilleumier et al.'s task, the attentional focus was alternating between stimuli with or without emotional content. As expected, in the gender judgment condition (attending faces), fearful faces evoked greater response in a network of regions associate with emotion processing, including the AMY. However, this differential activation was not present when subjects performed the more difficult peripheral (bar-orientation) task, and thus did not attend to faces. Also, there were no differences in response times related to the fearful expression of the face distractors. Based on these findings, Pessoa et al. (2002) concluded that emotional information is differentially processed only when there are sufficient attentional resources that are not exhausted by a demanding concurrent cognitive task. In other words, emotional stimuli can "capture attention" if there are enough attentional resources "to be captured" and not engaged by other tasks at hand.

One possible cause for the continuing debate between the traditional and competing views is the fact that emotional content and task demands were not systematically manipulated within the same study, and thus studies supporting the traditional view may be criticized for not using challenging enough tasks to deplete attentional resources (Anderson et al., 2003; Luo et al., ; Vuilleumier et al., 2001), and the studies supporting the competing view can be criticized for

not using powerful enough emotional stimuli to "capture" attention (Mitchell et al., 2007; Pessoa, 2005; Pessoa, McKenna et al., 2002; Pourtois, Spinelli, Seeck, & Vuilleumier, ; Silvert et al., 2007). The automaticity or reliance on attention of task-irrelevant emotional processing cannot be fully understood unless the degree of emotional charge and the level of task demands are systematically manipulated within the same task. Hence, the main goal of the present investigation was to better understand the intricate nature of emotion-cognition interactions by manipulating both the emotional charge of distracting information and the demands of the main cognitive task.

It should be noted, however, that the traditional and the competing views concerning emotion processing are not necessarily mutually exclusive, as processing of emotional information can be both automatic and modulated by attention. Typically, the degree of attentional demand necessary to complete a task has been manipulated by varying the size of stimulus array, the stimulus attributes (Lavie, 1995), and the difficulty in discriminating stimulus orientation (Pessoa et al., 2005). However, another way of manipulating the difficulty of information processing is by varying the amount of time information is available to process (Grill-Spector & Kanwisher, 2005). Studies employing the later manipulation point to differences in the processing of emotional stimuli as a function of their exposure duration, and show that different stages during the time course of emotion processing may vary in their susceptibility to modulations by attention (Luo et al., 2010; Rotshtein et al., 2010; Smith, 2008), with automatic processing of emotional information occurring only during shorter presentation times (White, 1995). This evidence highlights the complex relationship between emotion, attention and awareness, and suggests that the two seemingly opposing views concerning basic emotion processing may in fact not be mutually exclusive – i.e., depending on the circumstances

emotional information can be processed automatically but can also benefit from engaging available attentional resources. However, to our knowledge, the effect of stimulus duration on task-irrelevant emotional distraction under varying degrees of perceptual load has not been previously investigated. Such an investigation can provide a possible understanding of the time course of emotion processing that could reconcile the two opposing views.

Elucidation of these matters depends on investigation of the neural correlates of emotion-cognition interactions in conditions where emotional and cognitive processing are in competition with each other. In addition to AMY, a number of other brain regions have been identified as being part of an emotion processing network, including lateral and medial prefrontal cortical (PFC) regions, anterior cingulate cortex (ACC), as well as other brain regions susceptible to emotional modulation (e.g., perceptual areas, such as visual cortex) (Adolphs, 2002; Anders, Lotze, Erb, Grodd, & Birbaumer, 2004; Anderson et al., 2003; Dolcos, Iordan, & Dolcos, 2011; Dolcos, LaBar, & Cabeza, 2004; Dolcos & McCarthy, 2006; Fichtenholtz et al., 2004; Grimm et al., 2006; Kober et al., 2008; Phan, Fitzgerald et al., 2004; Phan, Taylor et al., 2004; Phan, Wager, Taylor, & Liberzon, 2004; Phillips, Drevets, Rauch, & Lane, 2003; Sabatini et al., 2009; Wang, McCarthy, Song, & Labar, 2005; Yamasaki, LaBar, & McCarthy, 2002). In conditions of competing emotion-cognition interactions, the neural system involved in 'hot' emotional (*HotEmo*) processing interplays with a neural system involved in 'cold' executive (*ColdEx*) processing, which includes brain regions that are part of the so-called fronto-parietal attentional network, underlies the ability to stay focused on task-relevant information and is important for cognitive control (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002; Duncan & Owen, 2000; Ochsner & Gross, 2005).

Dissociating Neural Responses Reflecting Detrimental Impact of vs. Reduced Emotional Distraction

Although previous investigations identified the role of *HotEmo* brain regions in various aspects of emotion processing and emotion-cognition interactions (Dolcos et al., 2011), less is known about their involvement in the response to emotional distraction associated with the detrimental impact on behavioral performance versus those involved in minimizing the impact of such distraction on performance, especially when examining emotional distraction during lower-level perceptual tasks (but see Dolcos, Kragel, Wang, & McCarthy, 2006; Dolcos & McCarthy, 2006) for emotional distraction and cognitive control in higher-level working memory tasks). In previous studies with emotional distraction (Denkova et al., 2010; Dolcos et al., 2006; Dolcos & McCarthy, 2006), the role of brain regions whose activity was differentially sensitive to the presence of emotional distraction was further elucidated by examining brain-behavior relationships reflected in co-variations of brain activity with task performance. These investigations showed that brain areas of the *HotEmo* system where activity co-varied negatively with task performance were associated with responses reflecting increased distraction (Denkova et al., 2010), whereas areas of the *ColdEx* system where activity co-varied positively with task performance or decreased distractibility were associated with responses reflecting the engagement of cognitive control mechanisms to help cope with distracting emotions (Denkova et al., 2010; Dolcos et al., 2006; Dolcos & McCarthy, 2006). Therefore, the second main goal of the present investigation was to identify the neural correlates of emotion-cognition interactions in conditions where emotional information is presented as task-irrelevant distraction during a perception task, and to distinguish between their roles in responses reflecting the detrimental impact of vs. helping with emotional distraction.

The present study addressed these issues by using a perceptual orientation-discrimination task that allowed for the examination of the neural mechanisms that mediate the response to task-irrelevant emotional distraction. Brain activity was recorded using event-related fMRI while healthy participants performed this task that assessed the impact of emotional charge of distraction, perceptual load, stimulus duration, and their interactions on task performance.

Based on the two opposing views of how selective attention and emotion processing interact with each other, we made the following conditional predictions. First, regarding the behavioral effects, if the traditional view was correct, we predicted that automatic emotion processing would occur similarly, regardless of the amount of processing demands (high vs. low) required by the main task. On the other hand, if the non-traditional view was correct, we predicted that emotion processing would be modulated by the availability of processing resources – i.e., as processing demands of the main task increased, processing of task-irrelevant distraction (whether neutral or emotional) would decrease. However, if both views were correct, processing of emotional distraction would be both automatic and modulated by attention (i.e., behavioral data would show an effect of emotion regardless of the processing demand of the main task, but the effect of emotion would be larger when demand was low and more resources were available to process the task-irrelevant emotion). Second, regarding the neural correlates of these effects, if the traditional view was correct we predicted that processing of emotional distraction would be associated with activity in affective brain regions, and this activity would be present regardless of the processing demand of the main task. If the non-traditional view was correct, we predicted that processing of emotional distraction would be associated with greater activity in affective brain regions when processing demands of the main task were low. However, if both views were correct, we predicted that while overall processing of emotional

distraction would be associated with similar brain activity regardless of the processing demands, certain affective regions would show an increase in activity when the processing demands of the main task was low.

Finally, we also predicted a differential link with behavioral performance between regions associated with a detrimental impact of emotional distraction vs. reducing the impact of such distraction. Specifically, increased activity in regions of the *HotEmo* system linked to impaired performance would be associated with a negative impact of emotional distraction (Denkova et al., 2010), whereas increased activity in regions of the *ColdEx* system linked to enhanced performance would reflect the engagement of defensive mechanisms to help reduce the impact of emotional distraction (Dolcos et al., 2006; Dolcos & McCarthy, 2006).

Materials and Methods

Subjects. Eighteen (seven males) healthy right-handed young adults (19 –33 years of age; average age = 23.44; SD = 4.13) recruited from the University of Alberta and Edmonton City area, participated in the study. Participants signed an informed consent prior to participating and were reimbursed for their participation. The experimental protocol was approved for ethical treatment of human participants by the Health Research Ethics Board at the University of Alberta.

Task and Stimuli. Participants performed a perceptual orientation-discrimination task with distraction, in which participants made decisions on the orientation of vertical and horizontal pictures with varying degrees of emotional content (Figure 1). This task allowed the assessment of the impact of processing demand, emotional charge of distraction, and their interactions on the ability to make responses concerning the orientation (vertical vs. horizontal) of the rectangular pictures. Processing demand was manipulated by varying the ratio of the horizontal vs. vertical

sides of the rectangles, which influenced the difficulty in deciding whether the pictures were clearly rectangles (with vertical or horizontal orientation) or closer to squares (with uncertain orientation). There were a total of 280 rectangular pictures, 50% horizontal and 50% vertical). The vertical to horizontal (V:H) ratios were varied using increments/decrements of 0.006 around 1 (perfect square); the size of the starting square was 280 x 280 pixels. This resulted in 60 different rectangles with vertical to horizontal ratios ranging from 0.801 to 1.249, with a total of 30 horizontal and 30 vertical shapes. Among these, the 15 that were closest to a square (0.905 – 0.993, horizontal ratios and 1.007 – 1.113, vertical ratios) were classified as more difficult (high perceptual load), and the remaining 15 that were clearly rectangular (0.801 – 0.898 horizontal ratios, and 1.121 – 1.249 vertical ratios) were classified as less difficult (low perceptual load). Analyses of pilot data and the present results showed that this manipulation worked, as our results are comparable with those reported by studies supporting the competing view, where the emotion response was attenuated or eliminated under conditions of high attentional load (Pessoa et al., 2005). In addition, task demands were also manipulated by varying the presentation time of the stimuli (short = 250 ms vs. long = 1000 ms), which also influenced the difficulty of making the orientation decisions in the presence of concomitantly presented competing emotional information.

[Figure 1 about here]

Distraction level was manipulated by varying the emotional content of the rectangular pictures, and involved three main categories of pictures: emotionally negative (40%), emotionally neutral (40%), and scrambled (20%). Negative pictures were selected to stay consistent with previous research examining the automaticity of emotion (Pessoa, McKenna et al., 2002; Pessoa et al., 2005; Vuilleumier et al., 2001). The emotional and neutral pictures were

selected from the International Affective Picture System (IAPS, (Lang, Bradley, & Cuthbert, 2008), based on their normative scores for arousal and valence, and were supplemented with in-house pictures used in previous studies (Dolcos & McCarthy, 2006; Yamasaki et al., 2002). Next, the normative arousal and valence and scores (measured on a 9-point Likert scale), were combined to create a composite score that reflects the overall emotional charge of each picture, using the following formula: 9 - valence score + arousal score. To investigate possible finer emotion-related dissociations, in addition to the basic separation between emotional and neutral categories based on their composite scores, both picture types were further divided into two within-category subgroups, using a median split separation. This resulted in four picture categories according to their emotional content (i.e., high emotional (HiEmo), low emotional (LoEmo), neutral (Neu), and absolute neutral (AbsNeu)), which allowed for finer comparisons of the emotion effects by contrasting the most dissimilar conditions (i.e., HiEmo vs. least emotional/AbsNeu). The mean arousal, valence, and composite scores, respectively, were as follows: 6.4 / 2.2 / 13.2, for HiEmo pictures; 5.4 / 3.3 / 11.1, for LoEmo pictures; 3.7 / 5.0 / 7.7 for Neu pictures; and 3.0 / 5.1 / 6.9 for AbsNeu pictures. Pairwise comparisons found each of the emotional charge groups to be statistically significant from the others. Finally, the scrambled pictures were digitally scrambled versions of randomly selected emotional and neutral pictures (half from resulting from emotional and half from neutral pictures). The scrambled pictures served as a no-distraction controls as they had the same average spatial frequency and luminance as the emotional and neutral meaningful pictures. All pictures were presented in color. At the end of the study, participants also rated the emotional charge of emotional and neutral pictures, using a (9-point Likert scale; 1 = Lowest, 9 = Highest). Participants were instructed to rate as Lowest in emotional charge, those pictures that conveyed little to no emotional information and resulted

in the participants' feeling completely relaxed or calm, neutral and/or dispassionate. On the other hand, participants were instructed to rate as Highest in emotional charge those pictures that had high emotional content and made them feel stimulated, excited, emotionally negative, and/or passionate (see Supplemental Information for picture rating task and results).

Experimental procedures. The 280 trials were divided into seven runs of 40 trials (8 HiEmo, 8 LoEmo, 8 Neu, 8 AbsNeu, and 8 scrambled). Two different run orders were randomly assigned to the 18 participants to control for order effects. To avoid induction of mood states, the trials within each block were pseudo-randomized so that no more than two trials of the same valence type were consecutively presented. As illustrated in Figure 1, each trial started with the presentation of a rectangular picture for 250 or 1000 ms and was followed by a fixation screen for 1750 or 1000 ms, respectively. The subject's task was to indicate the orientation of the rectangular picture (i.e. vertical or horizontal) by pressing a button. Subjects were instructed to respond as quickly and as accurately as possible during the 2 second time window, beginning with the onset of the rectangular pictures. Immediately following this interval, a confidence screen was presented for 2 seconds, during which subjects rated the confidence of their orientation decision on a 3-point Likert scale (1 = lowest, 3 = highest). Confidence ratings were not considered in further analysis as performance was near ceiling for the low perceptual load condition. Each trial lasted 4 seconds [stimulus (2s) plus confidence rating (2s)], and was followed by a jittered fixation interval, drawn from an exponential distribution with a median of 6 seconds and a range from 4 to 12 seconds. Thus, the total trial length ranged from 8 to 16 seconds.

Imaging Protocol. MR scanning was conducted on a 1.5 T Siemens Sonata scanner. After the sagittal localizer and the 3D magnetization prepared rapid acquisition gradient echo (MPRAGE)

anatomical series (FOV = 256 x 256 mm; TR = 1600 ms; TE = 3.82 ms; number of slices = 112; voxel size = 1 mm^3), series of functional volumes allowing for full-brain coverage were acquired axially, using a gradient echoplanar sequence (FOV = 256 x 256 mm; TR = 2000 ms; TE = 40 ms; number of slices = 28; voxel size = 4 x 4 x 4 mm; FA = 90°).

Behavioral Data Analysis. Shape detection performance was measured as reaction time (RT) to making orientation discrimination decisions (vertical vs. horizontal) to the rectangular pictures. Repeated measures ANOVAs on RT and accuracy data were employed to assess the impact of emotional charge of distraction, perceptual load, stimulus duration, and their interactions on performance in the shape detection task. To compare the impact of rough vs. finer assessments of the emotional content, these analyses were performed on both the more comprehensive emotional categories (all emotional (All-Emo) vs. all neutral (All-Neu)) and on the most dissimilar emotional categories (HiEmo vs. AbsNeu). These analyses were performed on data from all 18 participants. Pairwise comparisons were Bonferroni corrected.

fMRI Data Analysis. Imaging data analyses were performed on 18 subjects, using SPM (Statistical Parametric Mapping) in conjunction with in-house custom Matlab scripts. Statistical analyses were preceded by the following pre-processing steps: quality assurance, TR alignment, motion correction, co-registration, normalization, and smoothing (8^3 mm Kernel). For individual analyses, task related activity was identified by convolving a vector of the onset times of the stimuli with a synthetic hemodynamic response (HDR) and its temporal derivative. The general linear model, as implemented in SPM2, was used to model the effects of interests and other confounding effects (e.g., session effects and magnetic field drift). Group analyses were conducted using random-effects models to assess the effect of distractor content, perceptual load,

and stimulus duration on emotion processing. Analyses focused on brain regions associated with both basic (e.g., AMY) and higher-level emotion processing (e.g., PFC).

The main goals of the present investigation were to investigate the traditional and non-traditional views concerning the interaction between emotion and selective attention, and to distinguish between the neural correlates of the response to the detrimental impact vs. reduction of emotional distraction, based on manipulating both the emotional charge of distracting information and the demands of the main cognitive task. To accomplish these goals, activity in brain regions specifically sensitive to the presence of emotional distraction, in conditions of manipulating perceptual load, stimulus duration, and their interactions on performance in the perceptual discrimination task was first investigated. Then, activity in these regions was tested for co-variations with RT data, to identify responses reflecting the detrimental impact of emotional distraction vs. the engagement of defensive mechanisms to help cope with distracting emotions. Increased activity to emotional distraction in emotion processing regions, coupled with positive co-variations with RT (slower responses), would be indicative of a detrimental impact of emotional distraction, possibly reflecting bottom-up effects. On the other hand, negative co-variations of activity in brain regions with RT (speeded responses), in response to emotional distraction, would probably reflect the engagement of top-down mechanisms, to cope with distraction. These analyses are described in detail below.

The Debate: The Traditional vs .Competing Views of Emotion and Attention

To investigate the traditional and non-traditional views of emotion and selective attention interactions when considering both emotional charge and attentional demand, we first assessed the effect of manipulating the degree of emotional charge on activation in emotion processing regions. To assess emotional distraction for a more comprehensive assessment, a t-map

contrasting All-Emo vs. All-Neu items was computed. To assess emotional distraction for the finer assessment, a t-map was computed that contrasted only HiEmo vs. AbsNeu items. Next, overlapping and non-overlapping brain regions were identified between the two assessments.

To examine brain regions susceptible to emotion processing that were modulated by manipulations of perceptual load (Load) or stimulus duration (Dur) we employed subtraction analyses. First, to assess emotional distraction for low and high Load, and short and long Dur separately, t-maps contrasting HiEmo and AbsNeu pictures were computed for when the task was performed under low load (Lo-Load), high load (Hi-Load), short Dur, and long Dur. Thus identifying voxels where HiEmo pictures produced greater activity than AbsNeu pictures for each condition. Then, to identify areas of brain activity where the amount of emotional distraction was affected by Load, the individual t-map for emotional distraction when Load was low or high was subtracted from the individual t-map for emotional distraction when Load was high or low, [((HiEmo Hi-Load > AbsNeu Hi-Load) - (HiEmo Lo-Load > AbsNeu Lo-Load)) ∩ (HiEmo Hi-Load > AbsNeu Hi-Load)] and [((HiEmo Lo-Load > AbsNeu Lo-Load) - (HiEmo Hi-Load > AbsNeu Hi-Load)) ∩ (HiEmo Lo-Load > AbsNeu Lo-Load)].

To identify areas of brain activity that were more susceptible to emotional modulation when Dur was short or long the individual t-map for emotional distraction when Dur was long or short was subtracted from the individual t-map for emotional distraction when Dur was short or long and, [((HiEmo Short Dur > AbsNeu Short Dur) - (HiEmo Long Dur > AbsNeu Long Dur)) ∩ (HiEmo Short Dur > AbsNeu Short Dur)] and [((HiEmo Long Dur > AbsNeu Long Dur) - (HiEmo Short Dur > AbsNeu Short Dur)) ∩ (HiEmo Long Dur > AbsNeu Long Dur)].

Dissociating Neural Responses Reflecting Detrimental Impact of vs. Reduced Emotional Distraction

To identify areas of brain activity reflecting the detrimental impact of vs. reduced emotional distraction, we performed brain-behavior correlations between activity in regions showing the particular effects corresponding to the significant behavioral results (i.e. the main effect of emotion and the emotional content x stimulus duration interaction) and RT data. Based on previous investigations, we expected that increased activity in regions of the *HotEmo* system linked to impaired performance would be associated with a detrimental impact of emotional distraction (Denkova et al., 2010), whereas increased activity in regions of the *ColdEx* system linked to enhanced performance would reflect the engagement of defensive mechanisms to help reduce the impact of emotional distraction (Dolcos et al., 2006; Dolcos & McCarthy, 2006).

To identify main effects in more comprehensive comparisons (e.g., All-Emo vs. All-Neu), an intensity threshold of $p < 0.001$ uncorrected was used, for finer assessments of main effects (e.g., HiEmo vs. AbsNeu), a threshold of $p < 0.005$ uncorrected was used, and for analyses assessing interactions (e.g., emotion x perceptual load), a threshold of $p < 0.05$ was employed. It should be noted that for all fMRI analyses the results of the direct contrasts were reported only if they survived additional independent masking procedures, and hence the activations in the resulting conjunction maps survived multiple criteria. For example, although an interaction (e.g., emotion x stimulus duration) an independent threshold of $p < 0.05$ was used, this corresponding statistical map was inclusively masked by the statistical map identifying a main effect of emotion on the long duration condition that survived an independent threshold of $p < 0.005$. Hence, the joint probability of the resulting conjunction map was of $p < 0.00025$, which is the product of their independent probabilities (0.05 x 0.005) (Fisher, 1950). Similarly, for correlation analyses involving double conjunctions, the joint threshold was also of $p < 0.00025$, resulting from the multiplication of the threshold for the correlation t-map ($p < 0.05$)

with that of the main effect map used to inclusively mask it with ($p < 0.005$). Details about the joint thresholds are provided in the legend of each Figure and Table. An extent threshold of 5 contiguous voxels was used in all analyses.

Results

Behavioral results

Reconciling the Debate: Emotion Effects are both Automatic and Modulated by Manipulations of Attention.

Discrimination Performance. When the distractors were analyzed as broad valence categories without consideration of emotional charge (i.e., All-Emo vs. All-Neu vs. Scrambled), as has been more commonly done in the existing literature, emotional content was not found to interact with task manipulations of attention (see Table 1 for a summary of mean reaction time and accuracy data). A main effect of Emotion and Load were found such that All-Emo distractors took longer to respond to compared to All-Neu distractors, and Hi-Load stimuli took longer to respond to compared to Lo-Load stimuli. These results confirm that emotional distractors were diverting resources from the main task and that rectangles with ratios closer to a square were harder to discriminate than those that were clearly rectangle. Importantly, this comprehensive assessment yielded no interaction effects between emotion and attentional demands (see Supplemental Information section for statistical details). These findings are consistent with the traditional view regarding emotion processing, as an impairing effects of emotional distraction was found regardless of the processing demands necessary to perform the main task.

[Table 1 about here]

Further investigation of behavioral data revealed that the emotional content of the distractors interacted with manipulations of processing demands only when a finer assessment of

emotional charge was considered. To test the effects of emotional charge, a 3-way repeated measures ANOVA on RT data was performed using only the most dissimilar emotional conditions (i.e. HiEmo vs. AbsNeu) and levels of Load and Duration. This finer assessment revealed a marginally significant Emotion by Duration interaction [$F(1,17) = 4.14$, $p = 0.058$, $\eta^2 = 0.2$], which was qualified by main effects of Emotion (HiEmo > AbsNeu, $F(1,17) = 11.35$, $p = 0.004$, $\eta^2 = 0.4$) and Load (Hi-load > Lo-load, $F(1,17) = 31.9$, $p < 0.001$, $\eta^2 = 0.65$), but not Duration. Post hoc analyses to elucidate this interaction revealed that it was driven by participants' longer RT for HiEmo compared to AbsNeu pictures when stimulus duration was long and Load was low, $F(1,17) = 5.83$, $p = 0.027$, $\eta^2 = 0.26$ (see Figure 2). These results confirm that the difference in magnitude in the emotional charge of the stimuli plays an important role in the effect of attention on emotion. Specifically, participants were more susceptible to emotional distraction when the difference in emotional content was the greatest (HiEmo vs. AbsNeu), there was more time for distraction (Long Dur), and the attentional resources were most available (Lo-Load). These findings are consistent with the competing view regarding emotion processing, and overall the behavioral results are consistent with both the traditional and the competing views.

[Figure 2 about here]

fMRI results

Dissociating Neural Responses Reflecting Detrimental Impact of vs. Reduced Emotional Distraction

Main Effect of Emotion. Overall, the behavioral results were consistent with both traditional and competing views and provide evidence that emotion processing is both automatic and modulated by manipulations of attention. This idea was also investigated in the analysis of brain imaging

data. First, to assess the impact of emotional charge of distraction we examined the neural correlates for the main effect of Emotion using both the more comprehensive assessment (All-Emo vs. All-Neu) and the finer assessment (HiEmo vs. AbsNeu). Comparison of these assessments revealed that regions susceptible to modulation by emotion (e.g., AMY, insula, and medial/inferior frontal gyri, fusiform and lateral occipital areas) underwent a larger degree of modulation when the most dissimilar emotional distractor conditions were considered (see Table 2). This was especially evident when investigating AMY activity where the strength of activation significantly decreased when using All-Emo vs. All-Neu distractors compared to when using only the extremes (see Figure 3). These results emphasize the role that the overall level of emotional charge and the relative difference between emotional and neutral conditions play in producing response in both basic (AMY) and higher-level (PFC) emotion processing brain regions.

[Figure 3 and Table 2 about here]

Importantly, these analyses also identified the neural correlates of responses reflecting the detrimental impact of emotional distraction, which parallels the main effect of Emotion observed behaviorally, supporting the traditional view. Given that overall emotional stimuli were associated with longer RT, increased activity in these regions may reflect longer processing time needed to make the orientation responses to these stimuli. Consistent with this idea, correlation analyses identified a significant positive co-variation between activity in the dorsomedial prefrontal cortex (dmPFC, BA 8/9) and the RT ($r = 0.52$, $p = 0.03$; peak voxel Talairach coordinates: $x = -5$, $y = 48$, $z = 34$). This finding suggests that activity in this area of the dmPFC is directly related to preferentially processing emotional over neutral stimuli and the subsequent distracting effects of emotion.

Effect of Processing Load on Emotion Processing. Given the fact that there might not be a one-to-one relationship between brain activity and behavior, we investigated how the manipulation of Load affected activity in brain regions susceptible to modulation by emotion, even in the absence of significant interactions (e.g., Emotion x Load) in behavioral results. Such an analysis revealed brain regions that reflect enhanced processing of emotion (HiEmo > AbsNeu) when processing Load was low compared to high (Lo Load > Hi Load, See Figure 4), and included the ventrolateral prefrontal cortex (vlPFC), medial prefrontal cortex (mPFC), lateral occipital cortex (LOC), and subcortical areas (i.e., ventral striatum) (see Table 3). Thus, while the behavioral data were not sensitive enough to detect changes in emotion processing as a function of Load, such changes were identified in the brain imaging data, as some areas susceptible to emotional modulation were more engaged when the processing demands of the main task were low and hence more resources were available for distraction. This finding provides support for the non-traditional, competing, view of emotion processing.

[Figure 4 and Table 3 about here]

Effect of Stimulus Duration on Emotion Processing. To further investigate the areas linked to the impairment of performance under manipulation of processing resources, the brain regions linked to modulation of emotion processing by increases or decreases of stimulus duration were then investigated (Emotion x Duration interaction). As expected, this analysis identified a number of brain regions differentially susceptible to emotional modulation for longer vs. shorter processing times (see Table 4). While certain emotion processing regions showed increases in emotion processing in response to both longer and shorter duration times (e.g., dmPFC, medial occipital cortex), other emotion processing regions (i.e., the dorsal ACC, vlPFC) were more susceptible to emotion under longer stimulus durations. As the pattern of activity in these latter regions

paralleled the behavioral pattern, we further investigated whether their engagement was linked to a detrimental effect of emotional distraction or to reduced emotional distraction, by co-varying activity in these regions with RT data.

[Table 4 about here]

These analyses identified a positive co-variation between activity in the right vlPFC (BA 45) and RT ($r = 0.65$, $p = 0.004$; peak voxel Talairach coordinates: $x = 51$, $y = 24$, $z = 7$). While this correlation was primarily driven by stimulus duration [i.e. no significant relationship was present in the same area for low ($r = 0.31$, $p = 0.22$) or high ($r = 0.25$, $p = 0.32$) Load], there was stronger activation present in this area under low, $t(17) = 2.56$, $p \leq 0.05$, compared to high Load, $t(17) = 1.66$, $p > 0.05$. This finding suggests that when more time is available for distraction, activity in the vlPFC is directly related to the distracting effects of task-irrelevant emotion on perceptual attention processing. Moreover, this region exhibited heightened sensitivity to emotional stimuli when attentional resources were not maximally engaged in a demanding task, and this was observed regardless of the effect of detrimental impact on behavioral performance (i.e., as was the case for Load).

On the other hand, a negative co-variation was identified in the dACC with the RT data ($r = -0.57$, $p = 0.01$). To determine if, as in the behavioral data, Lo-Load trials were driving this relationship we further examined the relationship between dACC activity and behavioral performance for Lo- and Hi-Load conditions. First areas of brain activity that corresponded with the interaction under Lo-Load were identified - activation in the dACC, LOC , and anterior insula (AI/vlPFC) was found to be strongest during such trials. Then, brain-behavior co-variations between these areas of activation and the RT data for these trials were assessed. These analyses revealed that activity in the dACC (See Figure 5) and LOC was negatively correlated

with the RT to HiEmo compared to AbsNeu distractors during Lo-Load and long duration trials ($r = -0.52$, $p = 0.03$ and $r = -0.62$, $p = 0.01$, respectively); importantly, this was not found for Hi-Load and long Duration trials ($r = -0.29$, $p = 0.24$ and $r = 0.20$, $p = 0.43$, respectively). These findings are consistent role of the ACC as a region sensitive to emotion-cognition integration and conflict resolution and with the role of the LOC (specifically BA 19) in object categorization.

[Figure 5 about here]

Taken together, these findings provide behavioral and neuroimaging evidence supporting both the traditional and non-traditional views of the interaction between emotion and selective attention, and point to brain regions whose activity was linked to a detrimental effect of emotional distraction on cognitive performance and to brain regions that helped reduce the effects of such distraction on cognitive performance.

Discussion

Using an experimental paradigm that manipulated both the emotional charge of distracting information and the demands of the main perceptual task, the present study yielded three main findings. First, consistent with both the traditional and the competing views, we found direct evidence that emotional information can be both processed automatically and susceptible to attentional modulations. However, emotional content and attentional load were only found to interact when finer assessments of emotional charge and processing demand were considered. Second, processing of emotional distraction was associated with increased activity in brain regions that are typically part of the emotion processing network (including AMY, lateral and medial PFC, and the occipital cortex), but activity in the dorsomedial PFC and ventrolaterall PFC was also associated with a detrimental impact of emotional distraction on cognitive performance. Third, we also found that activity in the dorsal anterior cingulate cortex (dACC) and the lateral

occipital cortex (LOC) was associated reduced emotional distraction. These findings will be discussed in turn below.

Reconciling the Debate: *Emotion Effects are both Automatic and Modulated by Manipulations of Attention*

Whether or not available attentional resources are needed for emotional information to be processed has been strongly debated in the recent emotion-cognition literature (Anderson et al., 2003; Erthal et al., 2005; Luo et al., ; Pessoa, ; Pessoa, McKenna et al., 2002; Pourtois et al., ; Vuilleumier et al., 2001; Vuilleumier & Driver, 2007). Here, we provide evidence that emotional information can be both processed automatically and is susceptible to attentional modulations. Specifically, in support of the traditional view, emotional stimuli generally elicited longer response times, suggesting that the emotional information inherent in the negative pictures was being similarly processed, regardless of manipulations of attentional demand. On the other hand, in support of the competing view, the detrimental effect of emotional distraction on the orientation discrimination task was found to be largest when most attentional resources were available (i.e., trials with low perceptual load and longer presentation time).

A critical aspect of our experimental design that made these findings possible was the involvement of finer assessments of the impact of emotional charge and processing demand. Regarding the emotional charge, one possible argument as to why in some cases emotion does not seem to be processed automatically is that finer assessments of emotional charge have not been taken into consideration. Indeed, while a main effect of emotional content was found in both the broad (all emotional vs. all neutral) and extreme (high emotional vs. absolute neutral) distractor analyses, the effect of emotion was stronger when isolating the extreme emotion conditions, and this effect was reflected at both behavioral and brain imaging levels (i.e., longer

RT for high emotional stimuli and greater activity in the emotion processing network, respectively). These finding suggests that to a degree, the emotional information inherent in the negative pictures was probably being automatically processed regardless of manipulations of attentional demand, which is supportive of the traditional view (Vuilleumier, 2005). Regarding the manipulation of processing demand, the detrimental effect of emotional distraction on the perceptual task was found to be largest not only when the emotional distraction was the most powerful but also when most attentional resources were available (i.e., trials with low perceptual load and longer presentation time). This finding suggests that processing of emotional information was partially dependent upon the amount of attentional resources available for distraction, and is thus supportive of the non-traditional view (Pessoa, 2005). The present findings also highlights the importance of task manipulations that consider both aspects that may influence performance in this task (emotional content and processing demand), as the debate over the automaticity of emotional processing is better informed here by examining various levels of the emotion and attention manipulations.

The neuroimaging data also presented evidence for both automatic and attention-regulated processing of emotional distraction. On the one hand, areas known to be involved in affective processing or to be sensitive to affective stimulation, including AMY, the lateral and medial PFC, insula, as well as perceptual areas (fusiform gyrus, LOC) showed greater activations to emotional compared to neutral distractors. Notably, activity in specific regions of this network was unaffected by manipulations of perceptual load and/or stimulus duration, which may reflect the automaticity of emotion processing and provide support for the traditional view of emotion-cognition interactions (Pourtois et al., 2010; Vuilleumier, 2005; Vuilleumier et al., 2001). On the other hand, not all affective processing regions were found to have activations that were

independent of manipulations of attention. Activations in specific regions (i.e. vlPFC, mPFC, LOC, and certain subcortical areas) were greater to highly emotional compared to absolute neutral trials during low perceptual load or long stimulus duration trials and were attenuated or no longer present when perceptual load was high or stimulus duration short. These changes in responsivity to emotional stimuli across manipulations of attention demonstrate that in some affective areas of the brain emotional processing is modulated by the amount of available attentional resources. These findings support the non-traditional, competing, view of emotion-cognition interactions that claims that emotional stimuli compete for processing resources with other stimuli (Pessoa, 2005; Pessoa, Kastner, & Ungerleider, 2002; Pessoa et al., 2005).

The fact that the latter activations were observed in the absence of a significant emotion-perceptual load interaction in the behavioral data point to the complexity of the interactions between the *HotEmo* and *ColdEx* systems, which does not always allow for a direct one-to-one relationship between brain and behavior. Nevertheless, these activations are valuable to consider, as differences in processing at the brain level may not always be reflected in overt behavioral measures. At any rate, the present behavioral and brain imaging findings provide direct evidence that the two views concerning basic emotion processing are not mutually exclusive and that depending on the circumstances emotional information can be processed automatically but is also susceptible to modulations linked to the availability of attentional resources.

Dissociating Neural Responses Reflecting Detrimental Impact of vs. Reduced Emotional Distraction: *Dorsomedial and Ventrolateral PFC Activity Linked to a Detrimental Impact of Emotional Distraction vs. Dorsal ACC and LOC Activity Linked to Reduced Emotional Distraction*

Among the regions showing overall increased sensitivity to the presence of emotional distraction, the dorsomedial PFC (BA 8/9) was also directly associated with the orientation discrimination performance, as expressed in the RT data. Specifically, activity in this region was positively correlated with the time needed to make the orientation discrimination decision to emotional compared to neutral distraction – as the RT to emotional relative to neutral distraction increased, activity in the dorsomedial PFC also increased. While a consistent functional role for mPFC as a whole has yet to be clarified (Etkin, Egner, & Kalisch, 2011), previous research with emotional distraction has found an increase in activation, or reduction in deactivation, in the mPFC (Denkova et al., 2010; Geday & Gjedde, 2009; Geday, Kupers, & Gjedde, 2007; Gjedde & Geday, 2009; Liberzon et al., 2007; Northoff et al., 2004), suggesting this area to be responsive to emotional interference. Moreover, the fact that the response of the mPFC to negative distraction was unchanged across levels of perceptual load and stimulus duration suggests that activity in this region may be linked to the ventral attentional network, which is an automatic, stimulus-driven, and bottom up system (Corbetta & Shulman, 2002; Fox, Corbetta, Snyder, Vincent, & Raichle, 2006; Kincade, Abrams, Astafiev, Shulman, & Corbetta, 2005; Posner & Petersen, 1990). This interpretation is consistent with evidence that activity in a similar dorsomedial PFC region was specifically associated with processing of emotional arousal, rather than valence (Dolcos et al., 2004), suggesting a role of this region in processing information with enhanced motivational relevance (Goldin, McRae, Ramel, & Gross, 2008; Gusnard, Akbudak, Shulman, & Raichle, 2001; Holzel et al., 2007; Lane, Fink, Chau, & Dolan, 1997; Lane et al., 1998; Northoff et al., 2000; Phan et al., 2003; Simpson, Snyder, Gusnard, & Raichle, 2001; Taylor, Phan, Decker, & Liberzon, 2003), which may explain longer response times associated with the response to negative distraction.

In addition to the dorsomedial PFC, the ventrolaterall PFC was also directly associated with orientation discrimination performance as measured by latency to respond. Activity in this region was positively correlated with response time to emotional compared to neutral distraction under long stimulus exposure durations compared to short durations, suggesting that increased activity in this region is associated with enhanced detrimental impact of the emotional distraction. This finding is consistent with evidence that this region is involved in reflexive orienting to motivationally relevant stimuli in the environment (Corbetta et al., 2008), and with evidence of its involvement in emotional perception, in general (Dolcos et al., 2004; Phan, Wager, Taylor, & Liberzon, 2002), and in the response to emotional distraction, in particular (Anticevic, Repovs, & Barch, 2010; Denkova et al., 2010; Dolcos et al., 2011; Dolcos et al., 2006; Dolcos & McCarthy, 2006)

The present study also provided evidence concerning the neural correlates of mechanisms engaged to reduce emotional distraction. In addition to the network of brain regions consistent with the main effect of emotional distraction mentioned above, the present study also identified brain regions linked to emotion x perceptual load x stimulus duration interaction observed in the behavioral data. This analysis identified the brain areas involved when emotional distraction produced the strongest effect (i.e., activations to highly emotional-low perceptual load and long stimulus duration trials), which included the dorsal ACC, IFG, and LOC. Further analyses elucidating the contribution of these regions to the observed effect, to relate their activations to the actual behavioral performance revealed that activity in both the dorsal ACC and LOC was negatively correlated with RT, which is consistent with an engagement of these regions to minimize emotional distraction.

Given the evidence concerning the role of dorsal ACC in top-down control, the present findings are not surprising. The ACC is an area of cortex commonly associated with conflict monitoring (Botvinick, Cohen, & Carter, 2004), and dorsal ACC is part of the dorso-parietal attention network (Bush, Luu, & Posner, 2000), associated with executive control (Corbetta et al., 2008; Corbetta & Shulman, 2002; Duncan & Owen, 2000; Ochsner & Gross, 2005). Additionally, dorsal ACC activity is systematically found in tasks with emotional and cognitive components (Phan et al., 2002), as well as in tasks in which emotional processing is modulated by manipulations of attentional demand (Mohanty et al., 2007; Whalen, Bush et al., 1998). Finally, ACC activity has been consistently found in tasks where, similar to the present study, goal-irrelevant emotional information is spatially contiguous with the target, such as the emotional Stroop task (Egner, Etkin, Gale, & Hirsch, 2008; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006; Haas, Omura, Constable, & Canli, 2006) and the emotional flanker task (Kanske & Kotz, 2010; Whalen, Bush et al., 1998).

In the context of the present task, due to the association with improved performance under conditions of high emotional distraction, the ACC and LOC response likely reflects the enhancement of task-relevant stimulus features (vertical / horizontal orientation), in order successfully cope with the presence of emotional distraction. This is consistent with evidence that LOC is an area of cortex commonly responsive to the perception and categorization of scenes and objects (Grill-Spector et al., 1999; Grill-Spector et al., 1998; Malach et al., 1995; Walther, Caddigan, Fei-Fei, & Beck, 2009), and hence it is reasonable to work jointly with ACC to help cope with emotional distraction when attentional resources are most susceptible to be "captured" by task-irrelevant emotional information. The idea that the ACC aids in coping with emotion is further supported by research demonstrating altered ACC reactivity to emotional

stimuli in individuals high in trait anxiety (Simmons et al., 2008), or with a diagnosis of post-traumatic stress disorder (PTSD) (Bremner et al., 2004; Shin et al., 2001), generalized anxiety disorder (Etkin, Prater, Hoeft, Menon, & Schatzberg, 2010), or major depressive disorder (MDD) (Halari et al., 2009).

It should be noted that while the present results provide valuable insight to the interaction between negative stimuli and attention, a limitation of this study is that interpretation of results is limited to negative stimuli. Only negative picture were involved to stay consistent with previous research examining the automaticity of emotion (Pessoa, McKenna et al., 2002; Pessoa et al., 2005; Vuilleumier et al., 2001), but given the evidence concerning valence-related differences in the impact of emotion on attention (Anderson et al., 2003; Beall & Herbert, 2008; Schupp et al., 2004; Shaw, Lien, Ruthruff, & Allen, 2011), examination of the impact of positive distraction would be valuable in understanding the role that valence plays in interacting with attention under various manipulations of perceptual load. Future studies should investigate whether the effects identified here also apply to positive distraction.

Conclusions

In sum, the present study provided direct evidence in support of both automatic and attention-dependent processing of task-irrelevant emotional information. As such, neither the traditional nor the non-traditional view of emotion-cognition interactions appears to fully account for the present results, which are instead consistent with both views. First, we found evidence that emotion processing occurs automatically, but is also influenced by the emotional charge of the stimuli used and by the amount of attentional resources available for processing. Second, we found evidence that while activity in the dorsomedial PFC and ventrolaterall PFC was linked to enhanced impact of emotional distraction, activity in the dorsal ACC and LOC

aided in reducing such distraction. Better delineation of the complex relationships between emotion and cognition not only has theoretical value in a broader context, but also lends insight into understanding affective disorders in which these relationships are dysfunctional, and possibly into understanding the mechanisms involved in the susceptibility to these clinical conditions.

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Table 2-1. Average Reaction Time (ms) and Accuracy (%) as a Function of Perceptual Load, and Stimulus Duration for All-Emo, All-Neu, and Scrambled Distractor Trials. All-Emo = All Emotional distractors; All-Neu = All Neutral distractors. n = 18

	Perceptual Load			
	Low		High	
	Stimulus Duration		Stimulus Duration	
Distractor Type	250 ms	1000 ms	250 ms	1000 ms
All-Emo				
Reaction Time	767.99	770.44	888.84	912.10
Accuracy (%)	95.00	91.40	70.90	70.00
All-Neu				
Reaction Time	730.83	703.62	847.06	839.99
Accuracy (%)	94.60	94.80	71.50	71.40
Scrambled				
Reaction Time	696.47	702.06	794.05	840.94
Accuracy (%)	97.70	93.90	82.30	66.50

Table 2-2. Heightened Emotional Response to Increased Emotional Charge. Overlapping and non-overlapping activity between comprehensive (All-Emo vs. All-Neu) and finer assessments (HiEmo vs. AbsNeu) of emotional reactivity. Analysis shows brain regions associated with emotional response are sensitive to the magnitude of difference in emotional charge between emotional and neutral stimuli. Overlapping activity = [(HiEmo > AbsNeu) ∩ (All-Emo > All-Neu)]. Non-overlapping activity = [(HiEmo > AbsNeu) exclusively masked by (All-Emo > All-Neu)]. The comprehensive assessment (All-Emo vs. All-Neu) did show any areas of activation that were not present in the finer assessment (HiEmo vs. AbsNeu). mPFC = Medial Prefrontal Cortex; dlPFC = Dorso-Lateral Prefrontal Cortex; vlPFC = Ventrolateral Prefrontal Cortex; MOC = Medial Occipital Cortex; BA = Brodmann Area; x, y, z denote coordinates in Talariach space; HiEmo = Highly Emotional; AbsNeu = Absolute Neutral; All-Emo = All Emotional; All-Neu = All Neutral. No asterisks denote significance at $p < 0.001$. *** Significance at $p < 0.005$. ** Significance at $p < 0.01$. *Significance at $p < 0.05$.

Brain Regions			Talariach Coordinates			T Values
		BA	x	y	z	HiEmo > AbsNeu / All-Emo > All-Neu
Overlapping Areas of Activation between (HiEmo > AbsNeu) and (All-Emo > All-Emo)						
mPFC	L. Superior / Medial Frontal	8	-9	43	44	5.08 / 2.20*
		6	-5	19	56	4.83 / 4.57
dlPFC	L. Middle Frontal Gyrus	9 / 46	-49	31	21	6.44 / 4.23
	R. Middle Frontal Gyrus	9	51	18	28	7.69 / 4.32
vlPFC	L. Insula / Inferior Frontal	13 / 45	-45	24	9	6.75 / 4.46
	L. Inferior Frontal Gyrus	47	-27	26	-12	6.28 / 2.51*
	R. Inferior Frontal Gyrus	47	21	26	-7	7.78 / 5.87
Cingulate	L. Cingulate Gyrus	24	-1	14	31	5.86 / 3.85
	R. Cingulate Gyrus	24	2	3	30	4.24 / 2.67**
	L. Posterior Cingulate Gyrus	31	-5	-53	24	5.46 / 2.25*
LOC	L. Inferior Temporal Gyrus	19	-49	73	0	12.30 / 8.60
	R. Inferior Occipital Gyrus	19	40	-76	-6	7.76 / 5.12
	L. Fusiform Gyrus	20	-38	-37	-18	9.53 / 6.95
		37	-38	-56	-13	6.41 / 5.00
	R. Middle Temporal Gyrus	39	54	-59	14	7.54 / 4.22
MOC	L. Lingual Gyrus	17	-12	-95	-5	6.3 / 4.03
	L. Cuneus	18	-24	-91	-1	4.34 / 3.09***
	R. Cuneus	18	17	-94	21	4.21 / 2.29*
	R. Middle Occipital Gyrus	18	21	-90	10	4.71 / 3.63***
Subcortical	L. Uncus	28	-23	5	-21	8.55 / 2.15*
	L. Amygdala		-19	-3	-18	6.45 / 2.83**
	R. Amygdala		14	-4	-14	8.45 / 3.43***
Non-overlapping Areas of Activation for HiEmo > AbsNeu						
Subcortical	L. Parahippocampal Gyrus	34	-23	4	-17	6.43
	L. Caudate Body		-9	1	11	3.42***
	L. Hippocampus		-30	-22	-16	5.24
	R. Putamen		21	14	-8	5.00
	R. Midbrain		10	-23	-9	4.70

Table 2-3. Brain Regions Sensitive to Emotion Processing and Manipulations of Load, Despite the Absence of Behavioral Differences. A number of brain regions sensitive to emotion processing were also differentially affected by load (low vs. high), even in the absence of behavioral evidence showing an effect of Load on emotional distraction. Top interaction = [(HiEmo Lo-Load > AbsNeu Lo-Load) vs. (HiEmo Hi-Load > AbsNeu Hi-Load)]. Top Mask = HiEmo Lo-Load > AbsNeu Lo-Load. Bottom interaction = [(HiEmo Hi-Load > AbsNeu Hi-Load) vs. (HiEmo Lo-Load > AbsNeu Lo-Load)]. Bottom Mask = HiEmo Hi-Load > AbsNeu Hi-Load. The joint probability of the resulting double conjunction maps was $p < 0.00025$ (resulting from $p < 0.05$ x $p < 0.005$, for the interaction and the masking contrasts, respectively). dmPFC = Dorsomedial Prefrontal Cortex; dlPFC = Dorsal Lateral Prefrontal Cortex; vlPFC = Ventrolateral Prefrontal Cortex; LOC = Lateral Occipital Cortex; BA = Brodmann Area; x, y, z denote coordinates in Talairach space; HiEmo = Highly Emotional; AbsNeu = Absolute Neutral; Lo-Load = Low Perceptual Load; Hi-Load = High Perceptual Load. No asterisks denote significance at $p < 0.001$. *** Significance at $p < 0.005$. ** Significance at $p < 0.01$. *Significance at $p < 0.05$.

Brain Regions			**Talairach Coordinates**			**T values**	
		BA	**x**	**y**	**z**	**Interaction**	**Mask**
HiEmo > AbsNeu Lo-Load > Hi-Load							
dmPFC	L Superior Frontal Gyrus	6	-2	27	54	2.78**	4.06
dlPFC	L Middle Frontal Gyrus	9	-46	19	27	3.29***	5.05
	R Middle Frontal Gyrus	46	51	22	25	2.81**	7.83
vlPFC	L Inferior Frontal Gyrus	9	-57	11	33	2.86**	4.63
	L Inferior Frontal Gyrus	45	-57	23	20	3.19***	4.41
	L Inferior Frontal Gyrus	46	-49	40	4	3.27***	3.50***
	R Inferior Frontal Gyrus	47	33	11	-12	3.37***	3.15***
Cingulate	L Poster Cingulate Gyrus	23	-1	-59	17	2.05*	2.94***
LOC	L Middle Occipital Gyrus	19	-38	-72	4	2.06*	6.50***
	L Middle Occipital Gyrus	37	-46	-65	-6	2.09*	6.48***
	L Fusiform Gyrus	37	-45	-60	-11	2.04*	3.08***
	R Middle Temporal Gyrus	22	54	-43	5	3.47***	3.89***
Subcortical	L Caudate Body		-9	1	19	3.60***	3.77***
	R Caudate Body		6	4	19	2.74**	2.99***
	L Uncus	28	-23	5	-21	2.60**	7.18***
HiEmo > AbsNeu Hi-Load > Lo-Load							
Cingulate	R Cingulate Gyrus	24	2	-4	29	2.22*	3.73
LOC	R Middle Occipital Gyrus	19	39	-74	9	2.48*	4.21

Table 2-4. Effect of Stimulus Duration on the Neural Response to Emotional Distraction. Unlike the pattern of activation observed with the manipulation of Load, where more regions were responsive to emotional distraction when Load was low, the manipulation of stimulus duration showed response to emotional distraction under both long and short duration times. Top table interaction = [(HiEmo Long Dur > AbsNeu Long Dur) vs. (HiEmo Short Dur > AbsNeu Short Dur)]. Top table mask = HiEmo Long Dur > AbsNeu Long Dur. Bottom table interaction = [(HiEmo Short Dur > AbsNeu Short Dur) vs. (HiEmo Long Dur > AbsNeu Long Dur)]. Bottom table mask = HiEmo Short Dur > AbsNeu Short Dur. The joint probability of the resulting double conjunction maps was of $p < 0.00025$ (resulting from $p < 0.05$ x $p < 0.005$, for the interaction and the masking contrasts, respectively). dmPFC = Dorsomedial Prefrontal Cortex; vlPFC = Ventrolateral Prefrontal Cortex; MPC = Medial Parietal Cortex; LOC = Lateral Occipital Cortex; MOC = Medial Occipital Cortex; BA = Brodmann Area; x, y, z denotes coordinates in Talairach space; HiEmo = Highly Emotional; AbsNeu = Absolute Neutral; Dur = Stimulus Duration. No asterisks denote significance at $p < 0.001$. *** Significance at $p < 0.005$. ** Significance at $p < 0.01$. *Significance at $p < 0.05$.

Brain Regions			Talairach Coordinates			T values	
		BA	x	y	z	Interaction	Mask
HiEmo > AbsNeu Long Dur > Short Dur							
dmPFC	L Medial Frontal Gyrus	6	-2	-7	58	2.68**	3.19***
vlPFC	L Inferior Frontal Gyrus	47	-34	29	3	2.35*	4.89
		13	-42	24	9	2.76**	5.68
	R Inferior Frontal Gyrus	47	25	18	-12	4.65	5.73
Cingulate	L Cingulate Gyrus	32	-1	14	38	4.11	3.69
Parietal	R Precentral Gyrus	6	36	-1	30	2.24*	4.17
LOC	L Inferior Occipital Gyrus	19	-38	-72	-3	2.88**	6.36
MOC	L Cuneus	18	-20	-96	2	2.24*	3.08***
Subcortical	R Thalamus		10	-16	-4	3.58***	3.24***
	R Midbrain		10	-4	-10	2.11*	5.41
HiEmo > AbsNeu Short Dur > Long Dur							
dmPFC	L Superior Frontal Gyrus	8	-13	35	54	2.60**	4.88
		8	-16	39	47	2.17*	2.93***
Insula	L Insula	13	-38	-26	23	2.62**	3.17***
	R Insula	13	44	-8	-7	4.23*	3.66
MPC	L Precuneus	31	-24	-71	19	3.47***	4.04
LOC	R Middle Temporal Gyrus	37	36	-60	17	2.07*	3.69
MOC	R Cuneus	18	17	-78	15	3.46***	3.09***
	R Middle Occipital Gyrus	19	28	-90	21	4.33	3.65
Subcortical	L Parahippocampus Gyrus	30	-20	-50	3	2.84**	3.25***
	L Caudate Tail		-20	-30	19	3.39***	3.04***

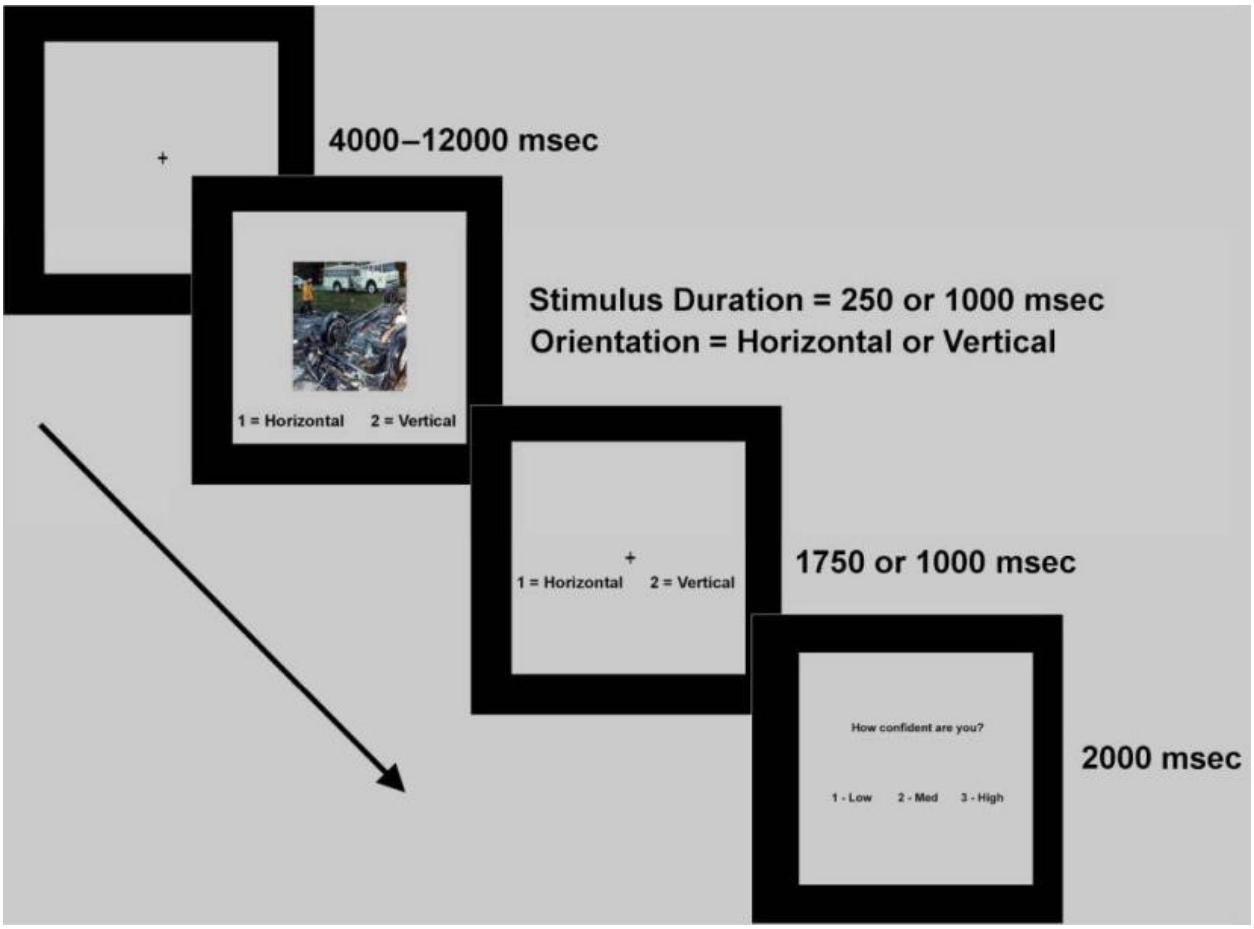

Figure 2-1. Diagram of the Perception Task Showing the Event Order for One Trial. Trial type was defined by the type of rectangular picture (HiEmo, LowEmo, Neu, AbsNeu, scrambled), the duration that the stimulus was presented (1000, 250 ms), and the perceptual load required to successfully perform the discrimination task (low, high). Participants were instructed to determine the orientation of the rectangular picture (1, horizontal; 2, vertical) and to maintain focus on the task. Participants then followed the orientation response with a confidence rating for their response. HiEmo = High Emotional; LoEmo = Low Emotional; Neu = Neutral; AbsNeu = Absolute Neutral.

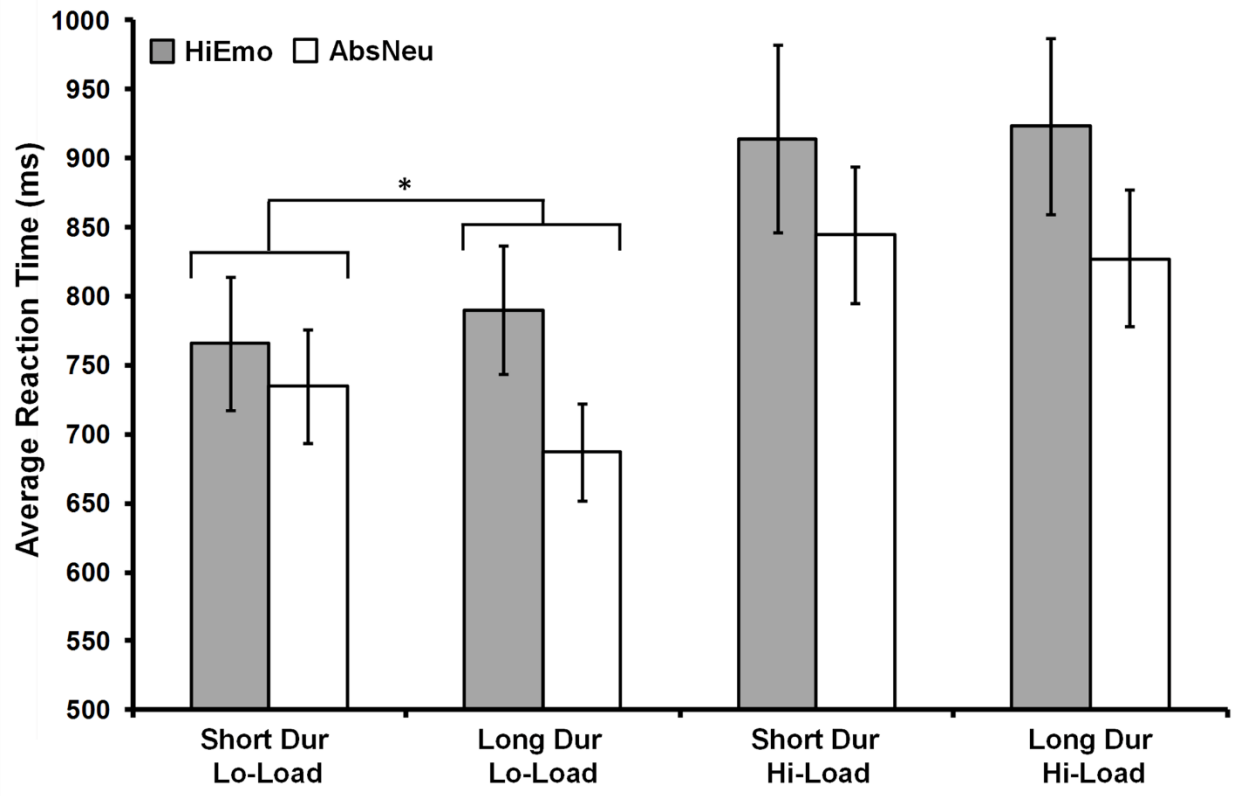

Figure 2-2. Emotional Distraction Augmented by the Availability of Attentional Resources. Figure shows average reaction time data for correctly identified rectangles. Trials with HiEmo distractors resulted in longer reaction time than those with AbsNeu distractors in all conditions, but also revealed an interaction between emotional content and stimulus duration that was driven by Lo-Load indicating the amount of emotional distraction was augmented when more attentional resources were available for distraction. Mean and standard error for each of the eight conditions were as follows: HiEmo, Lo-Load, Short-Dur (M = 765.37, SE = 48.27); AbsNeu, Lo-Load, Short-Dur (M = 734.46, SE = 40.88); HiEmo, Lo-Load, Long-Dur (M = 790.26, SE = 46.44); AbsNeu, Lo-Load, Long-Dur (M = 686.85, SE = 35.13); HiEmo, Hi-Load, Short-Dur (M =914.12, SE = 68.35); AbsNeu, Hi -Load, Short-Dur (M = 844.42, SE = 49.26); HiEmo, Hi -Load, Long-Dur (M = 922.89, SE = 64.2); AbsNeu, Hi -Load, Long-Dur (M = 827.37, SE = 49.97). HiEmo = High Emotional; AbsNeu = Absolute Neutral; Lo-Load = Low Perceptual Load; Hi-Load = High Perceptual Load; Dur = Duration. *interaction significant at $p < 0.05$, two-tailed.

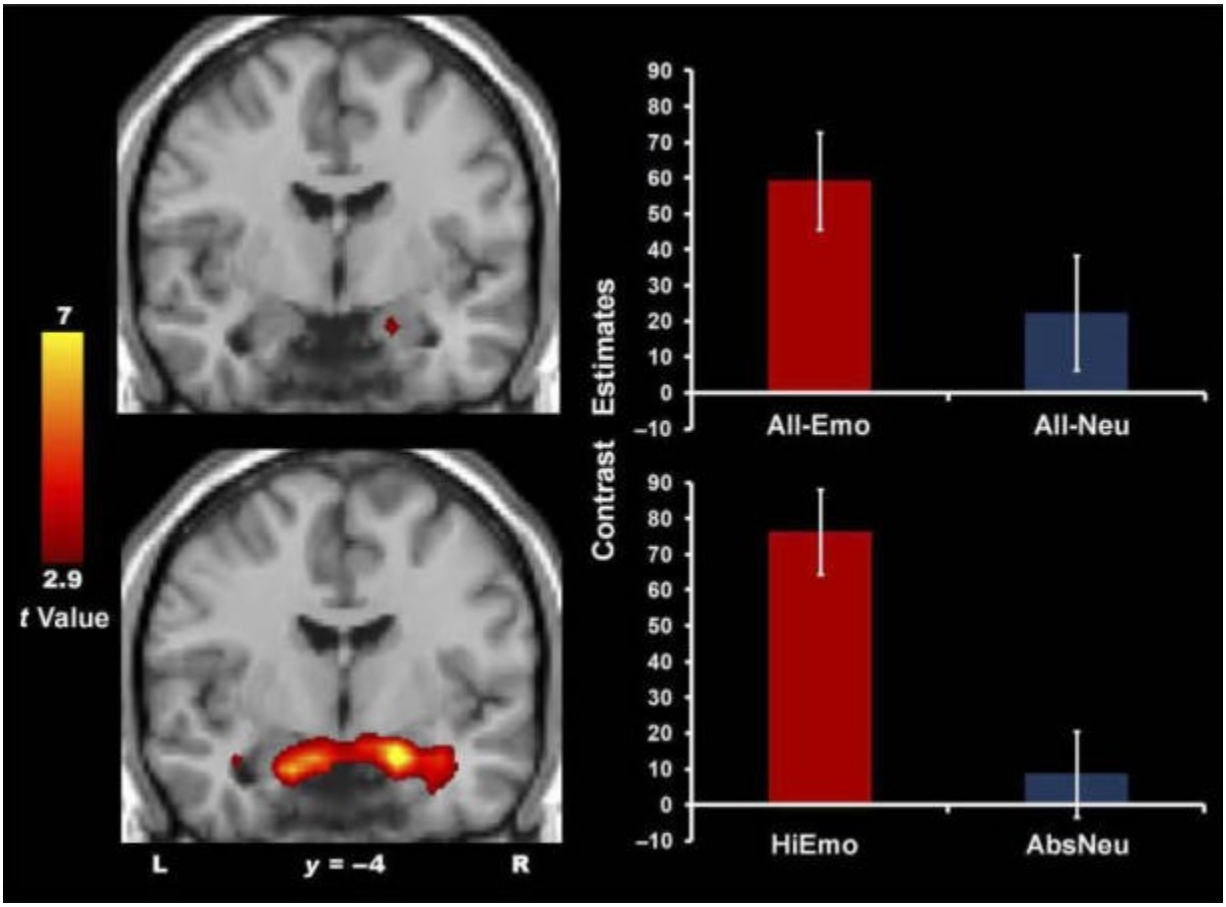

Figure 2-3. Amygdala Sensitivity to Emotional Charge: Increased Impact of Emotional Distraction when Pictures with most Dissimilar Emotional Charge are Compared. The figure highlights the importance of manipulations in emotional change when investigating alterations in basic emotion processing regions. The extent of amygdala (AMY) activation was dependent upon the degree of difference between the emotional and neutral picture content. The top left panel shows unilateral AMY activation (R. AMY, $t = 3.43$, $p < 0.005$) when All-Emo and All-Neu distractors were used for comparison, whereas the bottom left panel shows bilateral AMY activation surviving a higher threshold (R. AMY, $t = 8.45$, $p < 0.001$; L. AMY, $t = 6.45$, $p < 0.001$) when the most extreme distractors were selected for comparison (HiEmo vs. AbsNeu). The right side panels show the corresponding contrast estimates for these comparisons from the same peak voxel (Talairach coordinates: x = 14, y = -4, z = -14). HiEmo = Highly Emotional; AbsNeu = Absolute Neutral; All-Emo = All Emotional; All-Neu = All Neutral.

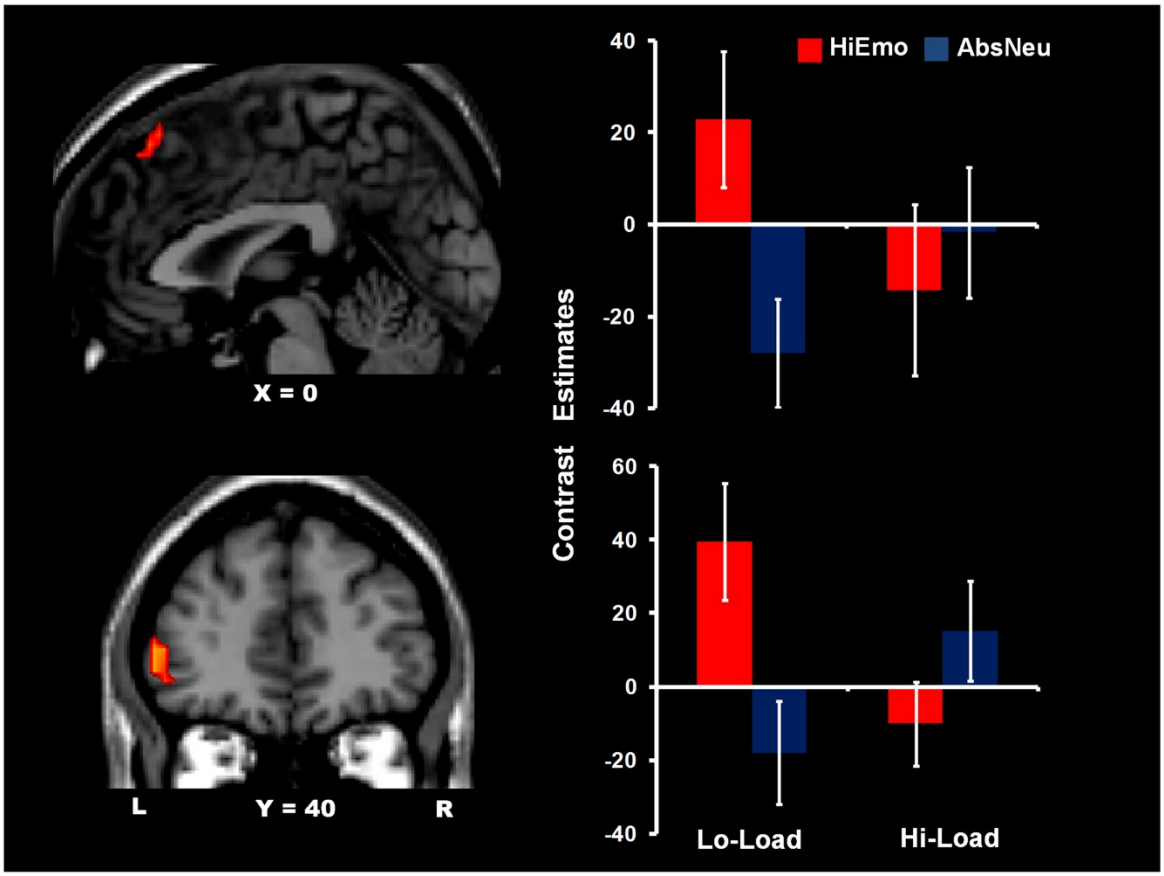

Figure 2-4. Dorsomedial and Ventrolateral PFC areas with Increased Susceptibility to Emotional Distraction Under Conditions of Low Attentional Demand. Image showing two brain regions where decreases in attentional demand of the main task resulted in increased susceptibility to emotional distraction. Specifically, areas of the medial and ventrolateral PFC were sensitive to emotional relative to neutral distractors only when the attentional demand necessary to perform the task was low. The left side panels show mPFC (top) and vlPFC (bottom) activations resulting from the Emotion x Load interaction where modulation by emotion only occurred under Lo-Load, and the right side panels show the corresponding contrast estimates for the peak voxels within these regions identified in the interaction analyses (L. mPFC, Talairach coordinates: x = -2, y = 27, z = 54; L. vlPFC, Talairach coordinates: x = -49, y = 40, z = 4). The double conjunction map resulted from the interaction t-map [(HiEmo Lo-Load – AbsNeu Lo-Load) vs (HiEmo Hi-Load – AbsNeu Hi-Load)], which was inclusively masked with the map identifying an effect of emotion in the Lo-Load condition (HiEmo Lo-Load – AbsNeu Lo-Load). The joint probability of this double conjunction map was $p < 0.00025$ (resulting from $p < 0.05$ x $p < 0.005$, for the interaction and mask maps, respectively). Similar patterns were also observed in the R. vlPFC, L. PC, bilateral LOC, and subcortical areas (See Table 3). HiEmo = Highly Emotional; AbsNeu = Absolute Neutral; Lo-Load = Low Perceptual Load; Hi-Load = High Perceptual Load. mPFC = Medial Prefrontal Cortex; vlPFC = ventrolateral Prefrontal Cortex; LOC = Lateral Occipital Cortex; PC = Posterior Cingulate.

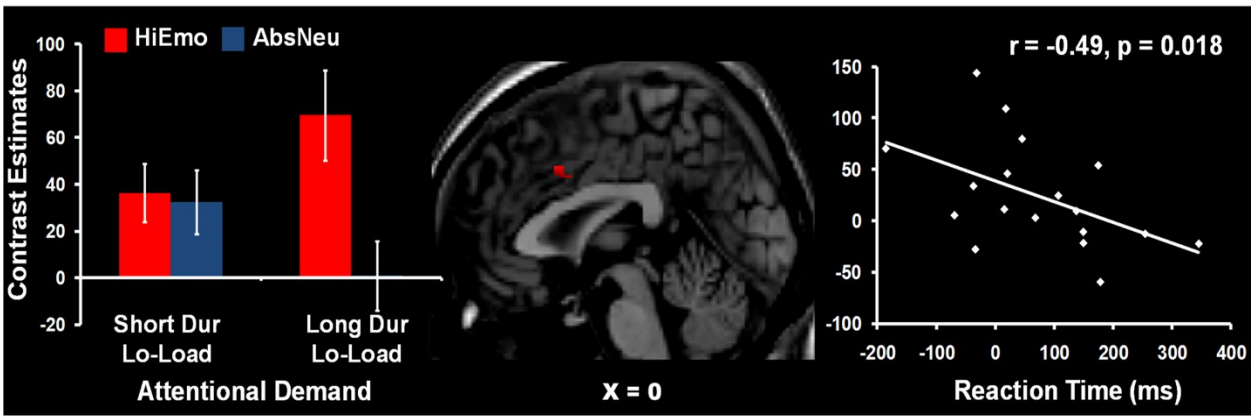

Figure 2-5. Dorsal ACC Activity Reflected Processing that Helped Diminish the Impact of Emotional Distraction. Of the regions that exhibited patterns of activity paralleling the behavioral results, where emotional distraction was greatest for long vs. short Dur under conditions of Lo-Load, only the R. ACC (BA 24) and L. MOG (BA 19) negatively co-varied with reaction time ($r = -0.49$, $p < 0.05$, $r = -0.62$, $p < 0.05$, respectively). The left and middle panels show the contrast estimates as extracted from the peak voxel in the R. ACC (Talairach coordinates: x = -1, y = 10, z = 33) where the interaction in brain imaging data that parallels the behavioral results was identified. The right panel shows a scatterplot illustrating the results of the correlation calculated on the contrast estimates from the peak voxel identified in the interaction analysis and the RT data. The triple conjunction map resulted from the correlation map described above, which was inclusively masked with the interaction t-map identifying the interaction that parallels the behavioral findings [((HiEmo Long Dur Lo-Load) – (AbsNeu Long Dur Lo-Load)) vs. ((HiEmo Short Dur Lo-Load) – (AbsNeu Short Dur Lo-Load))] and with the map identifying an effect of emotion in the long duration and low load condition. The joint probability of this triple conjunction map was $p < 0.0000125$ (resulting from $p < 0.05$ x $p < 0.05$ x $p < 0.005$, for the correlation, interaction, and effect of emotion maps, respectively)
Other brain regions paralleling the behavioral interaction (emotional distraction greatest for long vs. short Dur under conditions of Lo-Load) were found bilaterally in the AI (BA 13, L. AI, Talairach coordinates: x = -38, y = 20, z = 9; R. AI, Talairach coordinates: x = 29, y = 20, z = 14), L. ITG and FG (BA 37,Talairach coordinates: x = -42, y = -65, z = -3 and x = -42, y = -45, z = -19), L. MOG (BA 19, Talairach coordinates: x = -42, y = -81, z = 3), R. IFG (BA 47, Talairach coordinates: x = 36, y = 7, z = 31), and bilateral ACC (BA 32, L. ACC, Talairach coordinates: x = -1, y = 10, z = 38; BA 24, R. ACC, Talairach coordinates: x = 2, y = 3, z = 33). HiEmo = Highly Emotional; AbsNeu = Absolute Neutral; Lo-Load = Low Perceptual Load; Hi-Load = High Perceptual Load; Dur = Stimulus Duration; BA = Brodmann Area; ACC = Anterior Cingulate Cortex; MOG = Middle Occipital Gyrus; AI = Anterior Insula; ITG = Inferior Temporal Gyrus; FG = Fusiform Gyrus; IFG = Inferior Frontal Gyrus.

CHAPTER 3

THE IMPACT OF EMOTIONAL DISTRACTION ON MEMORY: LINKING THE IMMEDIATE AND DELAYED INFLUENCE OF EMOTIONAL DISTRACTION ON COGNITION

Neural Correlates of Opposing Effects of Emotional Distraction on Perception and Episodic Memory: An Event-Related fMRI Investigation

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An important question in the emotion literature concerns the relationship between the immediate impact of emotional distraction on perception and the long-term impact of emotion on memory. Typically, in the context of distraction and dual task paradigms, task-concurrent emotional distraction impairs task-relevant performance as the emotional information tends to capture and reallocate cognitive resources (Hodsoll, Viding, & Lavie, 2011; Kensinger & Corkin, 2003; Mitchell et al., 2007; Pottage & Schaefer, 2012; Talmi, Schimmack, Paterson, & Moscovitch, 2007; Vuilleumier, Armony, Driver, & Dolan, 2001). This has been thought to occur as a result of privileged processing for emotional information, due to its increased relevance for survival. It is not clear, however, how this initial processing of distracting emotional information influences memory for the distracters themselves, and what the neural mechanisms linking the immediate and long-term effects of distracting emotions are. The present study addressed this issue using functional magnetic resonance imaging (fMRI) and an experimental design that assessed both the immediate (*impairing*) and long-term (*enhancing*) effects of task-irrelevant emotional distraction.

The severity by which emotional distraction impacts perception has been shown to be influenced by two factors: the degree of cognitive demand or attentional resources required to perform the main task, and the degree of emotional challenge (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Mitchell et al., 2007; Pessoa, McKenna, Gutierrez, & Ungerleider, 2002; Pessoa, Padmala, & Morland, 2005; Shafer et al., 2012; Silvert et al., 2007; Vuilleumier, 2005; Vuilleumier et al., 2001). Previous research investigating these factors yielded mixed findings, consistent either with the view that emotion processing is automatic and independent of attentional resources (*traditional* view), or consistent with the view that emotion processing depends on manipulations that affect the availability of processing resources (*competing view*),

linked to the demands/difficulty of the main task. However, these studies have not involved systematic manipulations of both task difficulty and emotional challenge. A recent study investigating this issue in a 'lower-level' perceptual task that manipulated both of these factors provided evidence that processing of emotional distraction is both automatic and modulated by attention (Shafer et al., 2012), which is consistent with both views . Specifically, consistent with the traditional view, we found that overall emotional distraction impacted task performance regardless of the attentional demands necessary to perform the main task. However, consistent with the competing view, we also found that the highest level of disruption by emotional distraction occurred when most resources were available for distraction. These results suggest that two mechanisms contribute to the immediate impact of emotional distraction on perception: one rooted in automaticity and the other modulated by attention. What remains unclear is how these manipulations at perception affecting the immediate impact of emotion may also influence the long-term effects of emotion on memory.

Regarding the long-term impact of emotion on memory, extant evidence also suggests the existence of two routes contributing to the memory enhancing effect of emotion (Dolcos, Iordan, & Dolcos, 2011; Dolcos, LaBar, & Cabeza, 2004a, 2004b; Kensinger & Corkin, 2004; LaBar & Cabeza, 2006). One route, consisting of medial-temporal lobe (MTL) structures comprised of emotion-based (amygdala - AMY) and memory-based (hippocampal structures - HC) regions, is thought to operate more automatically and largely independently of resources at the time of encoding. The other route, involving prefrontal and parietal cortices, is thought to depend on the contribution of other processes to the memory-enhancing effect of emotion, such as working memory, semantic memory, and attention. Evidence supporting the dissociation between the automatic and mediated routes has shown, for instance, that the AMY-HC engagement is

associated with emotional memory following a shallow level of processing during encoding, whereas areas previously shown to be modulated by attention were more sensitive to emotional memory under a deep level of processing (Dolcos et al., 2011; Dolcos et al., 2004a, 2004b; Ritchey, LaBar, & Cabeza, 2011). Overall, these results lend support to the idea that the memory-enhancing effect of emotion can result from both automatic and mediated/attention-dependent mechanisms.

A main open question concerns the relationship between the immediate and long-term effects of emotion in conditions where emotional information is presented as task irrelevant distraction, especially given that both effects seem to engage automatic and mediated/attention-dependent mechanisms. Specifically, it is not clear whether there is a one-to-one relationship between the two opposing effects of task-irrelevant information on perception and memory – i.e., is there a direct link between the immediate (*impairing*) and long-term (*enhancing*) impact, such that the conditions in which emotional distraction produces the strongest immediate impact will also be translated in the strongest long-term impact on memory? If so, this would suggest that reallocation of processing resources by emotional distraction, overlapping with the initiation of processing leading to better memory for the distracters themselves, is the main mechanism linking the immediate/impairing and long-term/enhancing effects of task-irrelevant emotional information. Alternatively, it is possible that the link between the impairing and enhancing effects does not occur when the former effect is maximized, and hence would likely involve slightly different mechanisms.

Previous research investigating how immediate resource allocation relates to long-term memory via manipulations of the amount of resources allocated towards the to-be-remembered items has shown that divided attention at the time of encoding negatively influences how well

those items will be remembered compared to items encoded with full/non-divided attention (Craik, 2001; Hicks & Marsh, 2000; Uncapher & Rugg, 2005, 2008). However, similar manipulations with emotional stimuli have shown smaller decrements in memory performance when attention was divided, although this resilience in memory came at a cost, as performance on the primary task was disrupted by the presence of emotional distraction (Kensinger & Corkin, 2003; Pottage & Schaefer, 2012; Talmi et al., 2007). Overall, these findings suggest a direct relationship between the immediate and long-term impact of emotional distraction, possibly involving automatic mechanisms, although a role of mediated attention-related mechanisms is also implied. It is not clear, however, what the circumstances are in which a direct link between the immediate (impairing) and long-term (enhancing) impact of emotion can be found, what the neural correlates of the link between these opposing effects are, and how they are distinguished from those involved in one (immediate/impairing) or the other (long-term/enhancing) of these effects.

The overarching goal of the current study was to investigate the relationship between the immediate (impairing) and long-term (enhancing) effects of emotion by (i) examining how emotionally distracting information at perception influences the memory enhancing effect of emotion, and by (ii) identifying common and dissociable neural correlates of emotional distraction on perception and encoding success, thus linking the behavioral effects of emotional distraction and memory. These issues were investigated using a perception task involving manipulation of cognitive demand of goal-relevant processing in the presence of emotional distraction, followed by a surprise memory task for the distracters themselves, while event-related fMRI data were recorded.

Based on the extant evidence suggesting possible relationships between the immediate and long-term impact of emotional distraction, we made the following conditional predictions. First, regarding the behavioral effects, if there is a one-to-one relationship between the immediate/impairing and long-term/enhancing impact of emotion, we predict that the condition with the strongest immediate impact of emotion will produce the strongest long-term impact. Alternatively, if other factors also contribute to one or the other of these opposing effects, conditions where the immediate impact of emotion is present may not necessarily lead to a long-term impact of the same extent, and vice-versa. Regarding the neural correlates of these effects, if the same automatic and attention-mediated processes are involved in both the immediate and long-term effects and there is a one-to-one relationship between the two effects in the behavioral data, then we predict an overlap in the responses to the immediate and long-term impact of emotion in the same areas of the emotion network (e.g., AMY). However, if dissociable processes are involved in the immediate and long-term effects and there is no one-to-one relationship between the two effects, then we predict largely dissociable regions associated with the immediate and long-term effects of emotional distraction.

Materials and Methods

Participants

The present investigation involved analyses on data from 16 (7 males) healthy right-handed young adults (19-34 yrs.), recruited from the University of Alberta and Edmonton City area. Participants signed an informed consent form before participating, and were reimbursed for their participation. The experimental protocol was approved for ethical treatment of human participants by the Health Research Ethics Board at the University of Alberta.

Tasks and Stimuli

Participants completed two tasks, both performed in the scanner: a perceptual orientation discrimination task with distraction and an episodic memory task (see task diagram illustrated in Figure 1). In the perception task, participants made decisions on the orientation of vertical and horizontal pictures with negative and neutral content, and in the memory task they made decisions about whether emotional and neutral pictures were presented during the perception task or not. Since the focus of the current paper is on encoding success only fMRI data from the perception task were analyzed.

Perception Task. The stimuli and design of the perception task were described in a previous report focusing on the perceptual task (Shafer et al., 2012). Briefly, the task used pictures selected from the International Affective Pictures System (Lang, Bradley, & Cuthbert, 2008), based on their normative scores for arousal and valence and was supplemented with in-house pictures used in previous studies (Dolcos & McCarthy, 2006; Yamasaki, LaBar, & McCarthy, 2002). Distraction type was manipulated by the emotional content (negative vs. neutral) of the rectangular pictures. Attentional demand was manipulated by varying the presentation time of the stimuli (Short Dur = 250 msec vs. Long Dur = 1000 msec) and by varying the ratio of the horizontal vs. vertical sides of the rectangles (Lo-Load = clearly rectangles vs. Hi-Load = closer to squares). These two manipulations were chosen because both are considered manipulations of task demand (Grill-Spector & Kanwisher, 2005; LaBar & Cabeza, 2006), and to be consistent with research from both perception and memory domains. Specifically, a shorter presentation time (i.e., 250 msec) is consistent with investigations of the effect of processing load in studies of perception (e.g, Pessoa et al., 2002; Pessoa et al., 2005), while a longer presentation time (i.e., 1000 msec) is more consistent with paradigms investigating emotional memory (e.g., (Ritchey,

Dolcos, & Cabeza, 2008). Participants were instructed to maintain focus on the orientation task and determine the orientation of the rectangular shapes (1 = horizontal; 2 = vertical).

Recognition Task. Following the perception task, participants performed a recognition memory task for a subset of the pictures presented in the perception task. Of the total of 224 emotional (112) and neutral (112) pictures presented during the perception task, 160 (80 emotional and 80 neutral) were pseudo-randomly selected for the recognition memory task. Half of the 160 selected were Lo-Load and half were Hi-Load, and half were Short Dur and half Long Dur. This resulted in 20 emotional, Lo-Load, Short Dur; 20 emotional, Hi-Load, Short Dur; 20 emotional, Lo-Load, Long Dur; 20 emotional, Hi-Load, Long Dur; 20 neutral, Lo-Load, Short Dur; 20 neutral, Hi-Load, Short Dur; 20 neutral, Lo-Load, Long Dur; 20 neutral, Hi-Load, Long Dur. The 160 old images were pseudo-randomized with 80 new images selected from the same original picture databases and were selected on arousal and valence scores as well as similar semantic content. Averaged normative arousal and valence scores for Old and New emotional and neutral items, respectively, were as follows: 5.93/2.63 for Emotional old pictures; 5.95/2.66 for Emotional new pictures; 3.41/5.04, for Neutral old pictures; and 3.41/5.02 for Neutral new pictures. Arousal and valence scores were assessed using 9-poing Likert scales, as follows: Arousal (1 = Lowest / 9 = Highest), Valence (1 = Very Negative, 5 = Neutral, and 9 = Very Positive). Pairwise comparisons showed that emotional pictures had significantly greater arousal scores and lower valence scores than the neutral pictures, but there were no differences between the scores for emotional or neutral pictures from different categories.

[Figure 1 about here]

Experimental Procedures

The 240 trials were divided into 5 runs of 48 trials (16 Emotional old, 16 Neutral old, 8 Emotional new, 8 Neutral new). Old stimuli were pseudo-randomized based on when they appeared in the perception task to ensure that a delay of approximately 40 minutes occurred between the encoding and retrieval of a stimulus. For example, if a picture was presented in the first run of the perception task, then it would be presented in either the first or second run of the recognition task. Likewise, if a stimulus was presented in the last run of the perception task then it was presented in the last run of the recognition task. To avoid induction of longer-lasting mood states, the trials within each run were pseudo-randomized, so that no more than two trials of the same valence type were consecutively presented. Each picture was displayed for 2000 msec during which the participant had to indicate with a button press whether it was an '*Old*' or a '*New*' image. Immediately following this 2000 msec response window a confidence rating screen appeared for 2000 msec asking the participant to rate the confidence of their decision on a 3-point Likert scale (1 = lowest, 3 = highest). Each trial was followed by a jittered fixation interval drawn from an exponential distribution with a median of 6 sec and a range from 4 to 12 sec. Participants were not aware that a memory task would come following the perceptual task – they were told that the perception task would last for the entire time they were in the scanner. However, the perception task lasted approximately 55 minutes after which the experimenter instructed them that they would be performing a memory task for items that were presented in the perception task. The memory task did not begin until the participants confirmed that they understood the instructions for the task.

Imaging Protocol

Collection of MRI data was conducted on a 1.5-T Siemens Sonata scanner. After the sagittal localizer and the 3-D magnetization prepared rapid acquisition gradient echo anatomical

series (field of view [FOV] = 256 x 256 mm, repetition time [TR] = 1600 msec, echo time [TE] = 3.82 msec, number of slices = 112, voxel size = 1 mm^3), a series of functional volumes allowing for full-brain coverage were acquired axially, using a gradient echoplanar sequence (FOV = 256 x 256 mm, TR = 2000 msec, TE = 40 msec, number of slices = 28, voxel size = 4 x 4 x 4 mm, flip angle = 90°).

Behavioral Data Analysis

The immediate impact of emotion on perception was measured as reaction time (RT) to making orientation (vertical vs. horizontal) discrimination decisions to the rectangular pictures. An initial analysis was performed similar to that from the report focusing on the immediate effect of emotional distraction (Shafer et al., 2012), and involved a repeated measures ANOVA with three within subjects variables [Emotion (Emo, Neu); Load (Lo, Hi); Duration (Short, Long)]. However, to establish the link between the immediate and long-term effects of emotion, the present focus was on items that were both correct in the perception task and also later remembered in the memory task (Hits), and involved data from subjects that had at least 4 trials per condition (11 subjects met this criterion). This analysis was done to ensure that similar behavioral effects existed for the perception task after reducing the number of subjects and trials per subject as only items from the perception task that were also in the memory task were assessed. The long-term impact of emotion on memory was assessed as corrected recognition scores (% Hits - % False Alarms [FA]), using repeated measures ANOVA with the same three variables. Corrected recognition scores were involved because their calculation is a common and stringent technique of assessing accuracy in memory tasks, as it considers responses to both *Old* (Hits and Misses) and *New*/foil (Correct Rejections and False Alarms) items. Even though

confidence ratings were acquired during the recognition task, they were collapsed for analyses in order to increase statistical power.

Following these initial assessments on 11 subjects, to increase statistical power for both behavioral and fMRI analyses, data for the Load condition were collapsed together to maximize the possibility of comparing both the immediate and long-term effects of emotional distraction on perception and memory. In considering the main goal of the study (i.e., identification of common neural correlates of the opposing effects of emotional distraction), it was necessary to focus on conditions where the opposing effects of emotion were seen behaviorally, as this was the basis of our fMRI investigation. These opposing effects were identified in only one condition (i.e., Short Dur Hi-Load - see the third set of bars from left in the top and bottom panels of Figure 2). While, ideally, would have been to investigate the neural correlates of these opposing effects in the Hi-Load condition only, separation according to all conditions was possible only in data from 11 subjects. Hence, to increase the statistical power for brain imaging analyses, it was necessary to collapse the Load condition. This was the most valid choice for further analyses, as collapsing Load maintained the opposing effects (see first set of bars in Figure 3), and thus allowed us to perform the fMRI analyses corresponding to these behavioral effects on data from 16 subjects. Although collapsing Load might have overall weakened the effects observed in the fMRI data, seemingly driven by the Hi-Load condition (compare Figures 2 and 3), this was a necessary and advantageous trade-off, as it allowed for investigation of data from more subjects, although our sample size in this follow-up investigation (N = 16) was slightly smaller than what is suggested for the use of brain-behavior relationships (Lieberman, Berkman, & Wager, 2009), which we employed in the original report (N = 18) (Shafer et al., 2012). Furthermore, collapsing Load conditions was critical, as also described below, to identify brain activity associated with

the impact of emotion on memory using the subsequent memory paradigm (Dolcos et al., 2011; Dolcos et al., 2004b; Shafer, Iordan, Cabeza, & Dolcos, 2011), because it allowed analysis of data when considering Emotion (Emo vs. Neu), Duration (Short vs. Long), and Memory (Remembered vs. Forgotten) variables.

Again, when analyzing data from the larger sample (N = 16), to establish the link between the immediate and long-term effects of emotion in the behavioral data, the immediate impact of emotion was calculated on the items that were also later remembered in the memory task (Hits). The immediate and long-term effects of emotion were examined by performing a repeated measures ANOVA [Emotion (Emo, Neu); Duration (Short, Long)] on reaction time and corrected recognition data, respectively. Importantly, these analyses allowed us to examine how manipulations of attentional demand at encoding for task-irrelevant emotional items influenced emotion's long-term impact on memory. Pairwise comparisons were Bonferroni corrected.

fMRI Data Analysis

Imaging data analyses were performed on data from 16 participants, using SPM in conjunction with in-house custom Matlab scripts. Statistical analyses were preceded by the following preprocessing steps: quality assurance, TR alignment, motion correction, coregistration, normalization, and smoothing (8^3 mm Kernel). For individual analyses, task-related activity was identified by convolving a vector of the onset times of the stimuli with a synthetic hemodynamic response and its temporal derivative. The general linear model, as implemented in SPM2, was used to model the effects of interests and other confounding effects (e.g., session effects and magnetic field drift). There were 14 first-level regressors: 8 task variables (Emo Long Dur Hits, Emo Short Dur Hits, Neu Long Dur Hits, Neu Short Dur Hits, Emo Long Dur Misses, Emo Short Dur Misses, Neu Long Dur Misses, Neu Short Dur Misses) +

6 motion regressors (3 translations, 3 rotations). Group analyses were conducted using random-effects models to assess the effect of distracter content and stimulus duration on perception and memory processes. Based on the behavioral results and to increase statistical power, as mentioned above, the analyses of fMRI data assessed emotion's interaction with stimulus duration (Short vs. Long), which yielded the strongest effects of emotion on both perception and memory. Furthermore, to ensure that subjects had maintained focus on the primary task and also in accordance with the behavioral data where Hits were driving the main effect of emotion on perceptual performance, the fMRI data analyses for the immediate effect of emotion were performed on items presented during the perception task that were performed correctly in the perception task and that were later remembered (Hits). For the analyses of the long-term impact, subsequent memory effects were calculated for emotional and neutral items and then compared to each other (Dolcos et al., 2011; Dolcos et al., 2004b; A. Shafer et al., 2011). As with the analyses concerning the immediate effect of emotion, fMRI data analyses for the long-term effect only included items were correct in the perception task.

The main goal of fMRI data analyses was to identify the neural correlates linking the immediate impact of emotional distraction on perception and the long-term impact of emotion on memory, and the neural correlates specific to one or the other of these effects. To accomplish this goal, we compared activity in brain regions specifically sensitive to the presence of emotional distraction and activity in brain regions sensitive to the emotional enhancement of memory. First, paralleling the behavioral data, we investigated areas associated with emotional distraction for the short duration condition. A *t* map was computed contrasting short emotional (Emo Short Dur Hits) vs. short neutral (Neu Short Dur Hits) items.

Next, we investigated areas associated with the emotional enhancement of memory. Areas of brain activity reflecting the emotional enhancement of memory during encoding found for the short duration condition in the behavioral data were examined by employing subtraction analysis looking at differences in activity between remembered (Hits) and forgotten (Misses) items (Dm/Subsequent Memory Effect) for Emo Short Dur compared to Neu Short Dur stimuli. First we computed *t* maps for differences in activity due to memory for Emo and Neu Short Dur items separately [Emo Short Dur Dm = (Emo Short Dur Hits – Emo Short Dur Misses), Neu Short Dur Dm = (Neu Short Dur Hits – Neu Short Dur Misses)]. Then, to identify activity associated with the emotional enhancement of memory, we employed subtraction analysis where the individual *t* map for Neu Short Dur Dm was subtracted from the individual *t* map for Emo Short Dur Dm. To make sure that these differences were based on an existing Dm effect for the emotion condition and were not driven by negative Dm for the neutral condition, this interaction was then inclusively masked by Emo Short Dur Dm, [(Emo Short Dur Dm – Neu Short Dur Dm) ∩ (Emo Short Dur Dm)]. Lastly, to ensure that activity was unique to the behavioral effects found in the Short Dm condition, we exclusively masked the above resulting contrast with activity that was present when assessing emotional memory for the long duration condition, [(Emo Long Dur Dm – Neu Long Dur Dm) ∩ (Emo Long Dur Dm)]. As with the behavioral data, we collapsed confidence ratings in the fMRI analyses in order to increase statistical power. While this prevented us from disentangling similarities and differences between emotional distraction on recollection vs. familiarity memory processes, by separately examining high vs. low confidence responses (Daselaar, Fleck, & Cabeza, 2006; Hayes, Buchler, Stokes, Kragel, & Cabeza, 2011), we did find the majority of responses to be high in confidence and therefore our

data may be more indicative of recollection processes (confidence ratings distribution: high = 71%, medium = 20%, low = 9%).

After separately identifying the neural correlates of the immediate and long-term effects of emotion, we investigated brain regions that contribute both to emotion's initial impact on perception and attention and to emotion's enhancement of memory. To identify brain regions responsible for both effects, we examined overlapping areas of activation between the immediate and long-term impact of emotion using a conjunction analysis. This was performed using the contrast for the effect of emotion during perception for the Short Dur condition and the contrast for the emotional enhancement of memory during the Short Dur condition, [(((Emo Short Dur Dm – Neu Short Dur Dm) ∩ (Emo Short Dur Dm)), exclusively masked by ((Emo Long Dur Dm – Neu Long Dur Dm) ∩ (Emo Long Dur Dm))) ∩ (Emo Short Dur Hits > Neu Short Dur Hits)].

Finally, to dissociate areas that showed specificity only to immediate or long-term effects of emotion, we exclusively masked the contrasts computed above. For example, to identify activity associated only with the long-term effect of emotion, we exclusive masked the contrast associated with the long-term effect with that of the immediate effect and vice versa when identifying activity unique to the immediate effect. Also, to investigate the significance of overlapping or dissociating activations, brain-behavioral relationships were investigated by correlating brain activity with indices of performance (RTs for the immediate and Corrected Recognition scores for the long-term effects). These latter analyses targeted MTL emotion (AMY) and memory (HC) structures.

Cortical structures were assessed with a threshold of $p \leq 0.005$, uncorrected, and *a priory* MTL areas of interest were assessed with a threshold of $p \leq 0.05$; in addition, for all interaction analyses an intensity threshold of $p \leq 0.05$ was employed. These thresholds were selected to stay

consistent with our previous report using the same task (A. T. Shafer et al., 2012), so that similar inferences could be made across reports. It should also be noted that the interactions were masked by specific main effects using an intensity threshold of $p \leq 0.005$. Hence, the joint probability of the resulting conjunction maps was of $p \leq 0.00025$, which is the product of their independent probabilities (0.05 x 0.005; (Fisher, 1950). Similarly, for all interaction analyses examining MTL regions (i.e., AMY and HC) an intensity threshold of $p \leq 0.05$ was employed for the interaction, which was then masked by a specific effect using an intensity threshold of $p \leq 0.05$. Hence, the joint probability of the resulting conjunction map was of $p \leq 0.0025$. Finally, for correlation analyses in MTL emotion- and memory-related regions a threshold of $p \leq 0.05$ was used and all correlation maps were also masked by the statistical map that they were being correlated with. For example, in MTL regions for the immediate effect of emotion, a double conjunction was used where the correlation map ($p \leq 0.05$) was inclusively masked by the effect of emotion for the Short Dur condition ($p \leq 0.05$), resulting in a joint probability of $p \leq 0.0025$. Similarly, for the long-term effect of emotion a triple conjunction was used $p \leq 0.05$ for the correlation map, $p \leq 0.05$ for the interaction, and $p \leq 0.05$ for the Emo Short Dm, thus the resulting probability was $p \leq 0.000125$. Details about the joint thresholds are provided in the legend of each figure and table. An extent threshold of five contiguous voxels was used in all analyses.

Results

Behavioral Results

Direct Relationship between Immediate and Long-Term Impact of Emotional Distraction, in the Context of overall Dissociating Impairing vs. Enhancing Effects. Unlike the immediate impact of emotional distraction on perceptual processing, which was greatest when processing resources

were most available (easy task and long presentation time), the long-term impact of emotion on memory was the strongest when processing resources were least available (difficult task and short presentation time). Initial analysis (n = 11) on reaction time data for the immediate impairing effect of emotional distraction on perception showed a main effect of Emotion, $F(1,10) = 10$, $p = 0.01$, Load, $F(1,10) = 8.03$, $p = 0.02$, and an Emotion x Load x Duration interaction, $F(1,10) = 5.34$, $p = 0.04$. As previously found with a larger sample (Shafer et al., 2012), trials with negative distracters took longer to respond to than those with neutral distracters and Hi-Load trials took longer to respond to than Lo-Load trials. Furthermore, the three-way interaction was driven by an Emotion x Duration when Load was low, $F(1,10) = 5.59$, $p = 0.04$, but not high, $F(1,10) = 0.629$, $p = 0.45$ (see Figure 2, top panel). Analysis on corrected recognition data (n = 11) revealed a main effect of Load, $F(1,10) = 5.39$, $p = 0.04$, and Duration, $F(1,10) = 23.34$, $p \leq 0.001$, but no main effect of Emotion. However, a marginally significant Emotion x Load x Duration interaction was present, $F(1,10) = 3.82$, $p = 0.08$, and post-hoc analyses showed that this interaction was driven by an Emotion x Load interaction for short duration items, $F(1,10) = 7.84$, $p = 0.02$. Specifically, emotion significantly affected memory in the Hi-Load, $t(10) = 2.31$, $p = 0.04$, but not in the Lo-Load, $t(10) = 0.976$, $p = 0.35$, condition for Short Dur items (see Figure 2, bottom panel).

[Figure 2 about here]

As mentioned in Methods, to increase statistical power for both behavioral and fMRI analyses, data for the Load condition were collapsed together to maximize the possibility of comparing both the immediate and long-term effects of emotional distraction on perception and memory, respectively. This was critical to identify brain activity associated with the impact of emotion on memory using the subsequent memory paradigm (Dolcos et al., 2011; Dolcos et al.,

2004b; A. Shafer et al., 2011). Collapsing load allowed us to include 16 subjects in our behavioral and imaging analysis for the memory data.

Importantly, collapsing load allowed for identification with increased statistical power of common effects for the immediate (impairing) and long-term (enhancing) impact of emotion, which occurred for the short presentation time (250 msec) (see Figure 3). Emotional distracters that were later remembered had a significant effect on discrimination performance such that there was delayed reaction time when distracters were emotional compared to neutral, $F(1, 15) = 9.99$, $p = 0.006$. This effect of emotion was found for both short, $t(15) = -2.15$, $p = 0.05$, and long, $t(15) = -2.56$, $p = 0.02$, duration conditions (Figure 3, top panel). Examination of corrected recognition scores also with load conditions collapsed together, for the items that were presented previously as distracters during the perception task, revealed an effect of emotion only for the short condition $t(15) = 2.1$, $p = 0.05$ (Figure 3, bottom panel). Analyses also identified a significant main effect of duration, $F(1, 15) = 26.06$, $p \leq 0.001$, with memory performance being overall better for long versus short duration items.

[Figure 3 about here]

In summary, the behavioral data showed that the long-term impact of emotion on memory was the strongest when processing resources were least available, and both the immediate and long-term effects of emotion (albeit opposing) occurred for the short duration items. Hence, the fMRI analyses focused on identifying common and dissociable neural correlates associated with those items.

fMRI Results

Common Brain Regions for the Immediate and Long-Term Impact of Emotion. Investigation of overlapping effects of emotion on perception and memory in the Short Dur condition identified

common areas of activation in ventrolateral PFC (vlPFC), temporal-occipital cortex, in the left angular gyrus (AG), precuneus, and left amygdala (AMY) and hippocampus (HC) (see Figure 4 and Table 1).

[Figure 4 and Table 1 about here]

Hemispheric Disassociation in the Amygdala and Hippocampus Linked to Emotional Distraction and Memory. In addition to identifying brain regions associated with both the immediate and long-term effects of emotion on perception and memory, areas that dissociated between these effects were also identified. This analysis identified a hemispheric disassociation in the AMY and HC, which although showed bilateral activation in response to emotional distraction, showed memory-related activity only in the left hemisphere (see Figure 5). To further explore whether this disassociation was indicative of functional asymmetry, we extracted functional regions of interest (ROI) for the three clusters of activity identified in these regions for the long-term effect (i.e. left AMY, anterior HC, and posterior HC) and their homologous counterparts in the right hemisphere. Each functional ROI was comprised of the peak voxel of each cluster along with its neighboring voxels. We then conducted a repeated measures ANOVA with Emotion and Hemisphere as within subject variables for each of the three clusters. Results for the AMY and anterior HC clusters were similar and showed a main effect of Emotion [AMY, $F(1,15) = 6.39$, $p = 0.02$; anterior HC, $F(1,15) = 8.39$, $p = 0.01$], but no effect of Hemisphere or interaction between Emotion and Hemisphere. However, the posterior HC cluster, not only showed a main effect of Emotion, $F(1,15) = 5.63$, $p = 0.03$, but also an Emotion x Hemisphere interaction, $F(1,15) = 7.75$, $p = 0.02$). Post-hoc analysis revealed that differences between emotional and neutral short Dm were significant in the left, $t(15) = 3.96$, $p = 0.001$, but not right hemisphere $t(15) = 0.18$, $p = 0.86$. While the Emotion x Hemisphere interaction in the AMY and anterior HC

clusters was not significant, post-hoc examination showed the left hemisphere to indeed have stronger statistical difference between emotional and neutral short Dm compared to the right hemisphere; L. AMY, $t(15) = 2.87$, $p = 0.01$; R. AMY, $t(15) = 1.89$, $p = 0.08$; L. anterior HC, $t(15) = 2.81$, $p = 0.01$; R. anterior HC, $t(15) = 2.01$, $p = 0.06$.

Further investigation of activity in these regions using brain-behavior correlations revealed that the left AMY activity identified for the long-term effect of emotion on memory was correlated with the corresponding behavioral difference in memory performance, $r = 0.57$ $p \leq 0.05$ (Figure 5); activity in the left anterior HC (Talairach coordinates: x = -30, y = -7, z = -15) also correlated with memory performance, $r = 0.55$, $p \leq 0.05$, but the cluster size was less than 5 voxels. In addition, a positive brain-behavior co-variation was also identified between activity in the left entorhinal cortex (Talairach coordinates: x = -16, y = 4, y = -17) and RT during the perceptual task, but this effect was not specific to emotional distraction ($r = 0.7$, $p \leq 0.05$), as the same relationship was found for the neutral items ($r = 0.69$, $p \leq 0.05$).

[Figure 5 and Table 2]

Emotional Distraction vs. Memory-Specific Brain Activity. Analysis investigating specific response to the immediate vs. long-term impact also identified activity linked only to the immediate impact of emotional distraction. This analysis identified a number of brain regions to have general specificity or sub-regional specificity with certain regions contributing to both immediate and long-term effects or being only involved in the immediate impact of emotional distraction on perception. Sub-regional specificity was found in the superior frontal gyrus, angular gyrus, inferior frontal gyrus, post central gyrus, precuneus, cingulate gyrus, fusiform gyrus, inferior and middle temporal gyri, as well as left AMY, HC, and paraHC regions. For example, inferior frontal gyrus (Brodmann Area 45) was identified for involved in the immediate

and long-term impact, whereas Brodmann Area 47 was associated with only the immediate impact of emotional distraction on perception. Regions that exhibited specificity to the immediate effect of emotional distraction included, medial frontal gyrus, precentral gyrus, superior temporal gyrus, and middle occipital gyrus (see Tables 1 and 2).

Analyses investigating specific response to the immediate vs. long-term impact also identified activity linked only to the memory enhancing effect of emotion. Again, as with the immediate impact reported above, regional and sub-regional specificity were found. Sub-regional specificity was identified in the superior frontal gyrus, cingulate gyrus, and precuneus. Of the activity identified as being unique to long-term impact of emotion on memory only one region, the superior parietal lobe was solely specific to emotional memory.

Collectively, the analyses of fMRI data targeting activity associated with the conditions that had opposing effects of emotional distraction on immediate and long-term processing identified both areas of overlap and areas dissociating these two effects. The overlapping areas are involved in the mechanisms responsible for both the immediate/impairing impact of emotional distraction on perception and for the long-term/enhancing impact on memory for the distracters themselves. Areas dissociating between these two effects were found to do so with either regional or sub-regional specificity. These findings will be discussed in detail below.

Discussion

The present study used an experimental paradigm that manipulated the degree of resource availability for processing task-irrelevant emotional distraction, to determine how the initial impact of emotional distraction is related to the long-term impact on memory for the distracters themselves. Our study yielded three main findings. First, we observed a direct relationship between the immediate (impairing) and long-term (enhancing) impact of emotion, only under

conditions of limited resources during encoding. Second, linked to this behavioral effect, we identified a number of brain regions of the emotion network that were involved in both the immediate and long-term impact of emotion, including AMY-HC regions, the ventrolateral prefrontal, temporal-occipital, and inferior parietal cortices. Third, responses in specific regions and sub-regions differentiated between immediate and long-term effects of emotion, both in terms of overall activation and co-variation with performance. Medial frontal, precentral, superior temporal, and middle occipital gyri activity was specifically associated with the immediate impact of emotion, whereas activity in superior parietal cortex was specifically associated with the long-term impact of emotion on memory. Furthermore, left AMY co-variation with subsequent memory performance and a hemispheric asymmetry of posterior HC activity in contributing to subsequent memory performance suggest a disassociation in the hemispheric contribution of these regions to the impact of emotional distraction on perception and memory.

Direct Relationship between Immediate and Long-Term Impact of Emotional Distraction, in the Context of overall Dissociating Impairing vs. Enhancing Effects

The fact that a direct relationship between the immediate (impairing) and long-term (enhancing) impact of emotion only occurred under conditions of limited processing resources during encoding suggest that the immediate impact of emotional distraction does not translate into long-term effects in a one-to-one fashion. Thus, the conditions in which emotional distraction produces the strongest initial impact on perception do not necessarily lead to the strongest long-term impressions on memory for the distracters themselves. In other words, the aspects that we may remember most may not necessarily be those that initially distracted us while trying to perform a perceptual task. Instead, emotional distraction also produced a boost in

long-term memory only under conditions of limited processing resources, which as also discussed below suggest that the direct link between opposing immediate (impairing) and long-term (enhancing) effects of emotional distraction under these circumstances involves automatic mechanisms. The engagement of such mechanisms to process task-irrelevant emotional information presented concurrently with a perceptual task led to reallocation of processing resources by emotional distraction, which in turn initiated processing that also resulted in better memory for the distracters themselves.

The absence of a direct link between the two opposing effects when more processing resources are available does not exclude the possibility that automatic mechanisms of emotion processing are also involved in circumstances that do not lead to a long-term memory advantage for emotional distraction. It is possible that, when more resources are available for processing during encoding, there is more opportunity for the mediated mechanisms to come "online" and influence memory for both emotional and neutral items, and hence the benefit that both emotional and neutral information receives from the mediated influences overshadows the memory boost produced for the emotional information by the automatic mechanisms alone. As a result, emotion's impact on memory is diminished, although overall the memory performance is enhanced in conditions of increased engagement of mediated mechanisms at encoding (e.g., longer processing time). Although the effect of stimulus duration on memory is consistent with findings from research investigating the role of stimulus durations around this range (i.e. 250 to 1000 msec) on memory performance (Christianson & Fallman, 1990; Clark-Foos & Marsh, 2008; Hulme & Merikle, 1976), the absence of an emotion advantage is inconsistent with previous findings identifying such an effect within divided attention paradigms (Kern, Libkuman, Otani, & Holmes, 2005; Pottage & Schaefer, 2012; Talmi et al., 2007); it is

consistent, however, with previous studies using level of processing paradigms where memory for neutral items may be on par with that of emotional items for deep levels of processing (Jay, Caldwell-Harris, & King, 2008; Reber, Perrig, Flammer, & Walther, 1994).

Elimination of the memory advantage for the emotional stimuli encoded in conditions of enhanced contribution of the mediated mechanisms may be due to a similar boost in memory performance for the neutral items or due to the engagement of mechanisms that diminished the impact of emotion on memory. Regarding the first possibility discussed earlier, with more resources available for distraction it is possible that the addition of mediated processes may have also benefited the neutral items for instance due to the engagement of working memory, semantic processing, and attentional processing (Dolcos et al., 2011). Regarding the alternative possibility, given our experimental design in which emotional information was task-irrelevant and participants were instructed to focus on the main perception task, it may be the case that under long stimulus duration, participants engaged processing to diminish the impact of emotional distraction. Thus, while they could not avoid being initially distracted by them (as indicated by the RT data in the perception task), trying to diminish their initial impact might have interfered with the mechanisms necessary for the emotional boost in memory performance. Importantly, however, we did observe a one-to-one relationship when only limited resources were available during the initial processing of emotional distraction.

Common and Dissociable Brain Regions for the Immediate and Long-Term Impact of Emotion

Turning to the neural correlates of the link between the initial and long-term effects of emotional distraction on perception and memory, analyses of fMRI data identified a number of brain regions of the emotion processing network whose activity was linked to both the

immediate/impairing and long-term/enhancing impact of emotion. Consistent with the engagement of automatic mechanisms linking the two opposing effects, we identified overlapping activity in AMY-HC regions, which have been linked to both emotion perception (Sergerie, Chochol, & Armony, 2008) and emotional memory (Dolcos et al., 2004b).

Hemispheric Disassociation in the Amygdala and Hippocampus Linked to Emotional Distraction and Memory. Even though the functional ROI analysis did not confirm our impression of a hemisphere effect in the left AMY and anterior HC for the memory-enhancing effect of emotion, it did identify a hemisphere effect in the posterior HC. The general increased Emo Dm in the AMY and anterior HC is consistent with previous research (Dolcos et al., 2004b), and although there was no hemisphere effect in these two regions for the long-term effect, the increased statistical strength due to decreased variance in Emo Dm response observed in the left hemisphere comparisons, along with the left AMY brain-behavior co-variation, suggest a more consistent left hemisphere involvement in emotional memory for this task. This is consistent with findings from several studies of emotional memory (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Mickley & Kensinger, 2008; Mickley Steinmetz & Kensinger, 2009; Talmi, Anderson, Riggs, Caplan, & Moscovitch, 2008), although it is not consistent with findings of recent meta-analyses (Kim, 2011; Murty, Ritchey, Adcock, & LaBar, 2010), which did not identify patterns of lateralization in the amygdala linked to memory. One possibility is that in conditions of processing emotional information as task-irrelevant distraction the right amygdala engages rapidly, producing a phasic response to the global arousal properties of the stimulus, thus extracting only crude information to prepare for immediate action. On the other hand, the engagement of the left amygdala is associated with a tonic response reflecting the extraction of more specific information and elaborative processing of the emotional qualities of the stimuli,

which also contributes to enhanced memory (Glascher & Adolphs, 2003; Markowitsch, 1998; Phelps et al., 2001; Sergerie et al., 2008). Furthermore, and as suggested by the increased variance in the right AMY and anterior HC for Emo Dm, the lack of right hemisphere involvement in emotional memory in these regions might be due to increased susceptibility of their right hemisphere response to individual differences.

Emotional Distraction and Memory-Specific Brain Activity: Increased Medial Frontal, Precentral, Superior Temporal, and Middle Occipital Activation Linked to Enhanced Emotional Distraction and Increased Parietal Activation Linked to Enhanced Emotional Memory. Brain regions found to have specificity in response to emotional distraction or memory dissociate between areas that are susceptible to immediate emotional modulation from those that are susceptible to long-term emotional modulation. Importantly, these regions identify unique relationships that are specific to different points along the information processing timeline (i.e., more immediate relationships between emotion and perception and longer-term relationships between emotion and memory). While there were several areas that exhibited sub-regional specificity for these effects, further investigations using a more rigorous approach (e.g., anatomical ROIs) is necessary to draw strong interpretations about these findings. As such, the current discussion will focus on identified regional specificity – i.e., activity in the medial frontal, precentral, superior temporal, and middle occipital gyri, associated only with emotional distraction, and activity in the superior parietal cortex, associated only with emotional memory.

Increased activation in the medial frontal gyrus (BA 10) linked to the immediate impact of emotional distraction on perception is consistent with a large body of research showing sensitivity of this region in response to emotional stimuli (Keightley et al., 2003; Scheuerecker et al., 2007), possibly reflecting increased motivational significance of emotional stimuli (Dolcos et

al., 2004a). Activity in the precentral gyrus has been reported in a number of studies of emotion processing (e.g., Canli, Desmond, Zhao, & Gabrieli, 2002; Keightley et al., 2003; LaBar, Gatenby, Gore, LeDoux, & Phelps, 1998; Morris et al., 1998; Scheuerecker et al., 2007; Wicker et al., 2003) although in most investigations this area was not the main the focus of investigation and hence typically was left out of discussion. Studies discussing its role, though, have suggested a role of this region in motor control/imagery associated with viewing emotionally arousing stimuli (Canli et al., 2002; de Gelder, Snyder, Greve, Gerard, & Hadjikhani, 2004) or with imitating emotional expressions (Lee, Josephs, Dolan, & Critchley, 2006). Although the superior temporal gyrus activity identified here is too inferior to be included in the temporal parietal junction (TPJ), its involvement is consistent with evidence linking activity in this region with attentional re-orienting associated with processing task-irrelevant emotional distraction(Corbetta & Shulman, 2002; Frank & Sabatinelli, 2012; Vuilleumier & Driver, 2007), and with evidence linking TPJ activity with sustained visual spatial attention towards the emotionally distracting stimuli (Thakral & Slotnick, 2009). Lastly, increased middle occipital activity likely reflects a boost in visual processing received by emotional items linked to increased extrastriate processing mediated by both cortical-cortical and subcortical-cortical mechanisms (Vuilleumier & Huang, 2009).

Turning to the areas associated only with emotional memory, it is interesting to note the effect observed in the superior parietal cortex dissociated from that identified in the inferior parietal lobe, which was present in both the immediate and long-term effects of emotional distraction. Considering these results in the framework of stimulus-driven versus goal-directed attention networks (Corbetta & Shulman, 2002), the present results are consistent with the idea that memory benefits from both increased bottom-up contributions through inferior parietal

activation (possibly reflecting capture of attentional resources) and top-down involvement from superior parietal cortex (possibly indicative of goal-relevant processing). Given that the target and distracter were contiguous and presented simultaneously, the superior parietal activity for items that were later remembered may be the result of goal-relevant processing resources being allocated to the item as a whole, and thus the emotional distracters benefited under conditions where an increase in goal-relevant resources was needed to successfully perform the task (i.e., short stimulus duration). The contribution of the superior parietal cortex to the long-term effect of emotional distraction is also consistent with event-related potential evidence that encoding processes contributing to enhanced memory for emotional events occur faster than for neutral events (Dolcos & Cabeza, 2002), presumably within a time window consistent with the present short duration. This evidence along with our findings suggest that parietal contribution to emotional memory may, in fact, be optimized under shorter exposure durations, perhaps indicating that its contribution can be more automatic than previously thought.

Conclusions

In summary, this study provided initial evidence for a direct link between the immediate and long-term impact of emotional distraction during a lower-level perceptual task in which the to-be-remembered items were task-irrelevant. First, a direct relationship between the immediate and long-term effects of emotional distraction was identified only under conditions of limited processing resources available at encoding. Also, the engagement of mediated mechanisms, once additional resources were available, diminished the effect of the automatic mechanisms on memory. Second, consistent with a role of automatic mechanisms linking these opposing effect, AMY-HC activity was common to both the immediate/impairing effect of emotional distraction and the long-term/enhancing impact of emotion on memory. Whereas a hemispheric

disassociation was identified in AMY and HC, with both sides associated with emotional distraction and left AMY and anterior HC linked to emotional memory, a clear asymmetry was identified in the posterior HC with only the left side contributing to successful encoding of emotional items. Third, brain regions were identified as being specifically susceptible to emotional modulation during distraction or memory formation, with activity in the medial frontal, precentral, superior temporal, and medial occipital gyri being linked to increased impact of emotional distraction, and activity in the superior parietal cortex being linked to better memory for emotional distracters. These findings demonstrate that the relationship between emotional distraction and memory is context dependent and that specific brain regions may be more or less susceptible to the direction of emotional modulation (*increased* or *decreased*), depending on the task manipulation and processes investigated. Understanding the mechanisms linking emotional distraction and memory offers important insight into clinical conditions, such as depression and anxiety, where both of these effects are dysfunctionally exacerbated.

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Table 3-1. Common Areas of Activation for the Immediate and Long-Term Effects of Emotion. Table identifies brain regions associated with the both the immediate (impairing) and long-term (enhancing) effects of emotion. Regions were identified by a conjunction map between separately identified regions for immediate and long-term effects. To make sure differences for the long-term effect of emotion were based on an existing Dm effect for the emotion condition and were not driven by negative Dm for the neutral condition, the long-term interaction was inclusively masked by Emo Short Dur Dm = (Emo Short Hits > Emo Short Misses). To ensure activity for the long-term effect of emotion was associated only with the behavioral effect seen for the Short Dur condition, the t-map for long-term effect of emotion for Short Dur was exclusively masked by the long-term effect of emotion for the Long Dur. Conjunction map = Immediate map [Emo Short Dur Hits > Neu Short Dur Hits] ∩ Long-term map [((Emo Short Dm) vs. (Neu Short Dm) ∩ (Emo Short Dm)), exclusively masked by ((Emo Long Dm) vs. (Neu Long Dm) ∩ (Emo Long Dm))]. lPFC = lateral Prefrontal Cortex; vlPFC = Ventral Lateral Prefrontal Cortex; PoCG = Post Central Gyrus; PC = Parietal Cortex; TOC = Temporal Occipital Cortex; MTL = Medial Temporal Lobe. T-values reported for cortical regions met the criteria of $p < 0.005$, $p < 0.05$, and $p<0.005$, for the immediate effect, long-term interaction and long-term mask, respectively; values reported for the MTL regions met the criteria of $p < 0.05$ for all effects.

Brain Regions		**Talairach Coordinates**				**T values**		
		BA	**x**	**y**	**z**	**Immediate**	**Long-Term** Interaction /Mask	**Cluster Size**
lPFC	R. Middle Frontal Gyrus	9	43	18	28	4.2	2.64/3.17	20
vlPFC	L. Inferior Frontal Gyrus	45	-45	28	13	5.08	5.6/3.63	49
	R. Inferior Frontal Gyrus	45	47	20	14	4.56	3.44/3.04	20
PoCG	R. Post Central Gyrus	43	54	-11	15	3.47	3.28/3.38	6
PC	L. Angular Gyrus	39	-50	-68	29	4.45	4.65/4.62	6
	L. Precuneus	7	-2	-57	35	3.68	3.23/3.47	7
TOC	L. Middle Temporal	21	-57	-47	6	4.02	3.28/3.68	15
	R. Middle Temporal	19	39	-75	19	4.29	3.09/3.19	19
	L. Inferior Temporal	37	-46	-65	1	4.15	1.91/3.53	5
	R. Inferior Temporal	19	40	-65	-5	4.32	2.78/3.91	26
	L. Fusiform Gyrus	37	-42	-50	-5	4.75	2.52/3.14	12
	R. Fusiform Gyrus	37	36	-49	-14	3.78	2.06/3.46	14
	R. Superior Occipital	19	35	-76	27	3.53	2.77/3.31	19
MTL	L. Amygdala		-27	-4	-15	3.05	2.49/1.82	21
	L. Hippocampus		-27	-39	-3	3.5	3.13/2.56	18
	L. Uncus	28	-23	8	-21	4.08	2.65/2.34	32
	L. Parahippocampus	34	-27	4	-14	4.5	3.37/1.87	32

		36	-34	-34	-14	3.65	2.32/2.41	18
Midbrai	L. Substania Nigra		-8	-12	-11	4.08	3.69/3.28	8

Table 3-2. Dissociable Areas of Activation for the Immediate and Long-Term Effects of Emotion. Table identifies brain regions associated with the either the immediate or long-term effect of emotion. Immediate effect = (Emo Short Dur Hits > Neu Short Dur Hits), exclusively masked by the long-term effect of emotion at $p < 0.05$. The long-term effect of emotion was found by calculating the interaction between Emo Short Dm vs Neu Short Dm. This interaction was then inclusively masked by Emo Short Dur Dm, to make sure the differences were based on an existing Dm effect for the emotion condition and were not driven by negative Dm for the neutral condition. To ensure activity for the long-term effect of emotion was associated only with the behavioral effect seen for the Short Dur condition, the *t*-map for long-term effect of emotion for Short Dur was exclusively masked by the long-term effect of emotion for the Long Dur. Long-term effect = [((Emo Short Dm) vs. (Neu Short Dm) ∩ (Emo Short Dm)), exclusively masked by ((Emo Long Dm) vs. (Neu Long Dm) ∩ (Emo Long Dm))]. Lastly, the entire long-term effect was exclusively masked by the immediate effect of emotion at $p < 0.05$. mPFC = Medial Prefrontal Cortex; lPFC = lateral Prefrontal Cortex; vlPFC = Ventral Lateral Prefrontal Cortex; PrCG = Precentral Gyrus; PoCG = Post Central Gyrus; PC = Parietal Cortex; TOC = Temporal Occipital Cortex; MTL = Medial Temporal Lobe. Significance threshold for the immediate effect of emotion is $p < 0.005$ and $p < 0.05$, for cortical and MTL regions, respectively. Significance threshold for the long-term effect of emotion is $p < 0.005$ for the mask for cortical regions and $p < 0.05$ for targeted MTL regions and $p < 0.05$ for the interaction for both cortical and MTL regions.

Brain Regions		**Talairach Coordinates**				**T values**		
		BA	**x**	**y**	**z**	**Immediate**	**Long-Term** Interaction /Mask	**Cluster Size**
Immediate								
mPFC	L. Superior Frontal Gyrus	8	-9	39	47	6.66		83
	R. Superior Frontal Gyrus	8	6	27	54	4.66		
	L. Medial Frontal Gyrus	10	-5	51	5	6.31		6
lPFC	L. Middle Frontal Gyrus	6 / 8	-39	10	44	3.95		13
vlPFC	L. Inferior Frontal Gyrus	47	-41	26	-8	4.12		6
		46	-42	40	4	5.6		29
	R. Inferior Frontal Gyrus	47	40	36	-2	3.96		43
Insula	L. Insula	13	-34	8	-14	5.30		83
PrCG	R. Precentral Gyrus	4	50	-6	44	3.89		7
PoCG	R. Postcentral Gyrus	3	28	-33	49	3.33		5
Cingulate	L. Cingulate Gyrus	31	-13	-25	45	4.86		20
PC	L. Inferior Parietal Lobe	40	-54	-39	43	3.6		7
	L. Precuneus	7	-35	-73	44	4.55		75
	R. Precuneus	7	17	-73	44	3.59		8
	L. Angular Gyrus	39	-53	-64	30	4		75
	R. Angular Gyrus	39	39	-76	30	3.51		5
TOC	L. Fusiform Gyrus	37	-49	-45	-12	4.80		80
		20	-34	-37	-18	4.72		

	L. Middle Temporal Gyrus	21	-49	9	-28	3.51		7
		37	-49	-66	4	4.65		47
	L. Inferior Temporal Gyrus	20	-49	-7	-19	3.76		13
	L. Superior Temporal Gyrus	22	-64	-36	7	3.93		16
	R. Middle Occipital Gyrus	18	28	-92	3	4.03		7
MTL	L. Amygdala		-19	-4	-14	2.85		30
	R. Amygdala		21	0	-17	3.21		41
	L. Hippocampus		-27	-19	-12	3.59		76
	R. Hippocampus		29	-23	-12	2.88		65
	R. Parahippocampus	28	25	-23	-12	3.72		8
		30	14	-35	-2	3.21		10
		34	25	4	-17	3.59		5
Subcortical	R. Thalamus-Pulvinar		17	-32	5	3.91		10
Midbrain	R. Substania Nigra		10	-23	-9	3.55		9
	R. Red Nucleus		6	-16	8	3.74		
Cerebellum	L. Culmen		-8	-46	-7	3.47		10
Long-Term								
mPFC	L. Superior Frontal Gyrus	9	-5	56	24		2.85/4.13	6
Insula	R. Posterior Insula		32	-29	13		2.33/3.37	5
Cingulate	L. Anterior Cingulate	32	-1	30	22		3.83/3.2	5
		24	-8	43	12		3.06/3.9	6
	R. Anterior Cingulate	32	3	42	16		2.9/3.03	6
PC	R. Precuneus	7	5	-74	55		3.17/3.25	8
	R. Superior Parietal Lobe	7	24	-65	35		3.04/3.32	7
	L. Superior Parietal Lobe	7	-17	-59	52		2.94/3.64	5
Subcortical	L. Putamen		-23	1	11		3.22/3.58	7

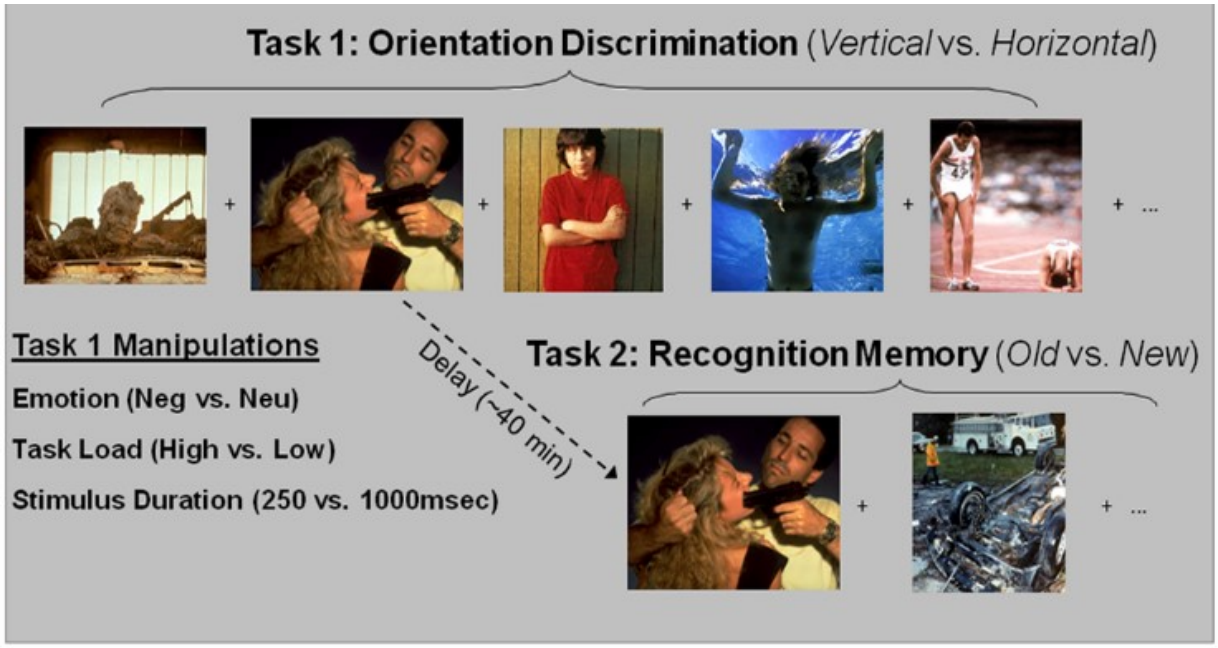

Figure 3-1. Diagrams of Perception and Memory Tasks. Trial type during the orientation discrimination task was defined by the type of distraction in the rectangular picture (Emo, Neu), the duration of the stimulus (250, 1000 msec), and the perceptual load necessary to perform the task (High, Low). Participants were instructed to determine the orientation of the shape. Following the perception task, participants were given a surprise recognition memory task for a sub-set of the distracters presented in the perception task. Participants were instructed to determine if the pictures were from the perception task 'Old' or were 'New', not presented during the perception task. Emo = Emotional; Neu = Neutral.

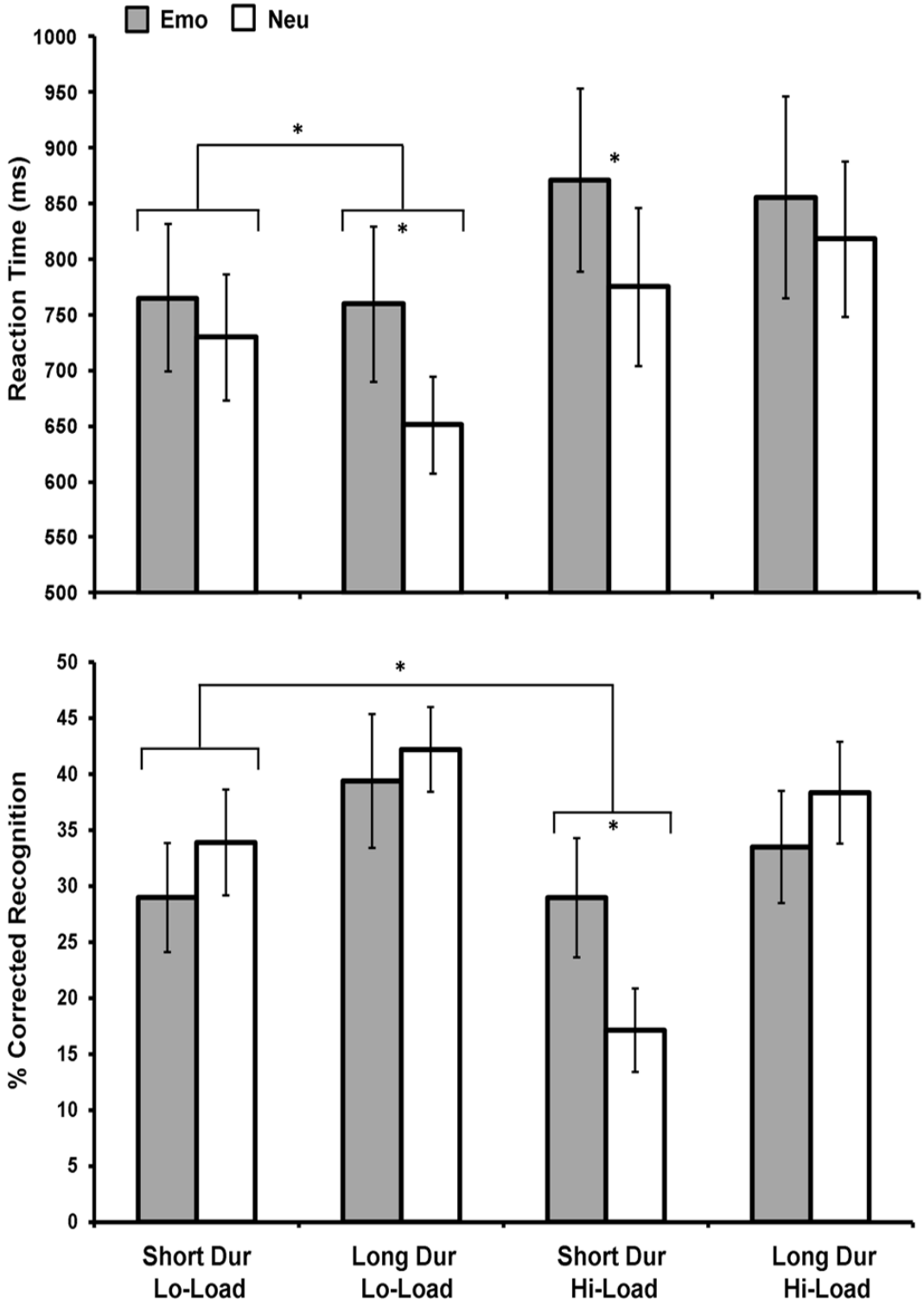

Figure 3-2. Emotional Distraction Impaired Perceptual Performance under Increased Availability of Processing Resources while Enhanced Memory for Task-Irrelevant Emotional Distraction Occured only Under Limited Processing Resources. Figure shows average reaction time (top panel) and corrected recognition data (bottom panel) for correctly

identified rectangles during the perception task for 11 participants. Impaired perceptual task performance for Emo distracters was greatest when resources were most available (under conditions of Lo-Load and Long Dur). Instead, enhanced memory for Emo distracters was found only when resources were the most limited (for Hi-Load and Short-Dur trials). An interaction was also found between emotion and load under short stimulus duration due to decreased memory for Neu distracters under conditions of limited resources, while memory for Emo distracters remained unaffected. Emo = Emotional; Neu = Neutral; Lo-Load = Low Perceptual Load; Hi-Load = High Perceptual Load; Dur = Stimulus Duration. *significant at $p \leq 0.05$, two-tailed.

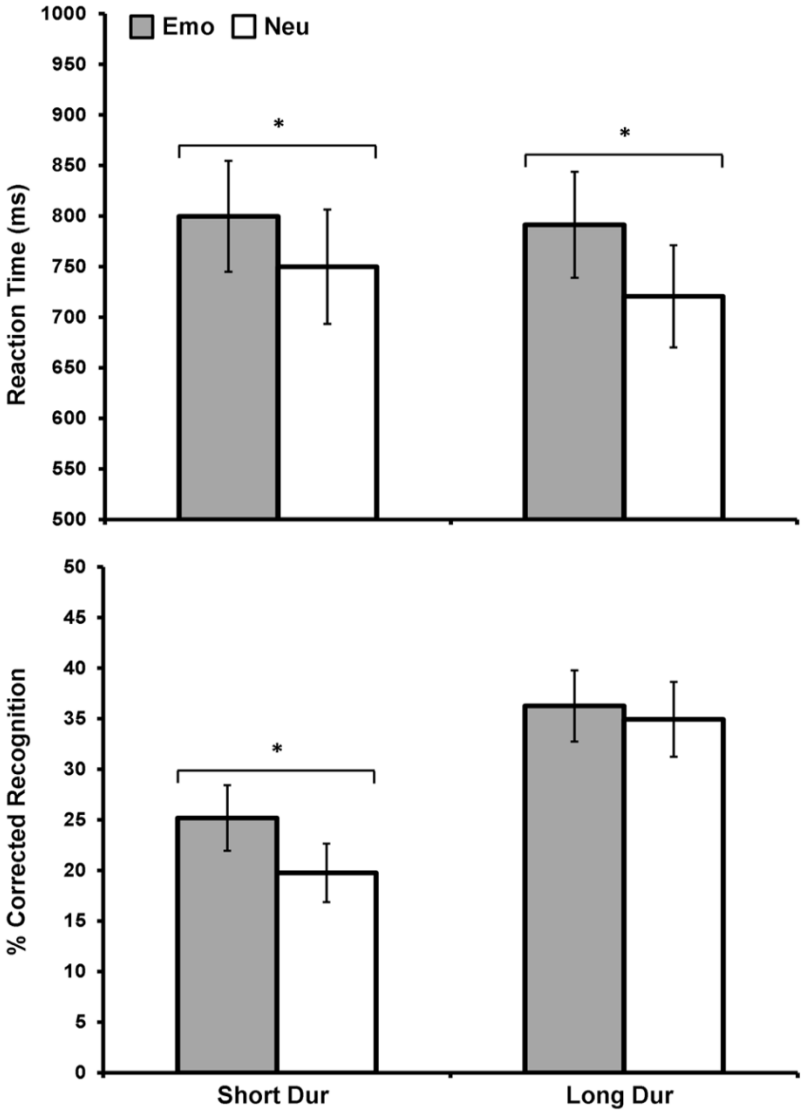

Figure 3-3. Direct Relationship between Emotional Distraction and Memory, under Limited Resource Availability. Figure shows the item categories meeting both criteria – impaired perception and enhanced memory - for 16 subjects, after collapsing the Load variable. Top panel shows average response latency data for correctly identified rectangles that were later remembered. Bottom panel shows average corrected recognition data for the same items. As illustrated, the left side of the two graphs shows the direct relationship between emotional distraction and memory under limited resources during encoding, by identifying the items for which the opposing immediate/impairing vs. long-term/enhancing effects co-occur. Although these opposing effects are driven by the Hi-Load condition (as evident in Figure 2), it was necessary to collapse Load to increase power for analyses of brain imaging data using the subsequent memory paradigm. Emo = Emotional; Neu = Neutral; Dur = Stimulus Duration. *significant at $p \leq 0.05$, two-tailed.

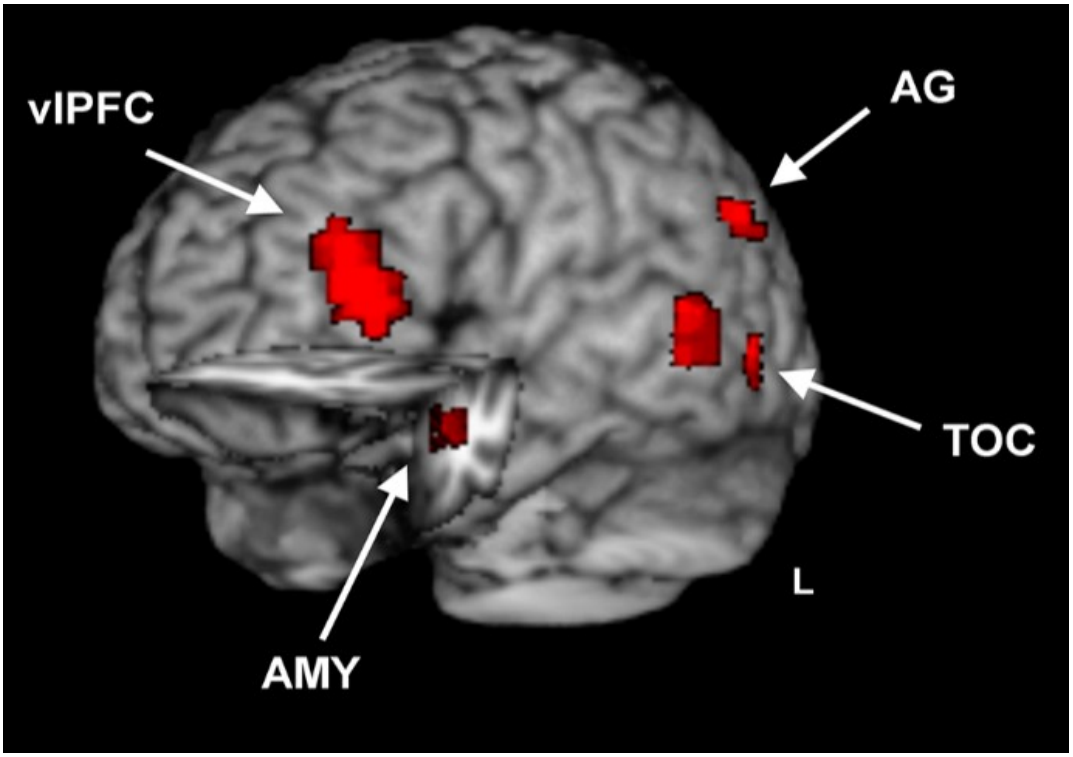

Figure 3-4. Brain Regions Sensitive to Opposing Emotional Modulation during Emotional Distraction vs. Memory. Image shows common regions of response to the impairing effect of emotional distraction and the enhancing effect of emotional memory, superimposed on a high resolution brain image displayed in a tridimensional view using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/). Cut-out in the left hemisphere also reveals similar response to emotional distraction and memory in the left AMY and anterior HC. The conjunction activation maps contributing to the overlap were identified separately for immediate/distraction and long-term/enhanced memory for the short Dur condition. The maps contributing to the final conjunction map were separately created for the immediate and long-term impact, which each resulted from maps with $p < 0.005$, $p < 0.05$, $p < 0.005$ for the main effect of emotion, interaction, and mask maps, respectively, for areas outside of the MTL, and $p < 0.05$, $p < 0.05$, and $p < 0.05$ for the main effect of emotion, interaction, and mask maps, respectively, for areas within the MTL (AMY, HC); see Methods section for details. vlPFC = ventrolateral Prefrontal Cortex; TOC = Temporal Occipital Cortex; AG = Angular Gyrus; AMY = Amygdala; HC = Hippocampus; L = Left.

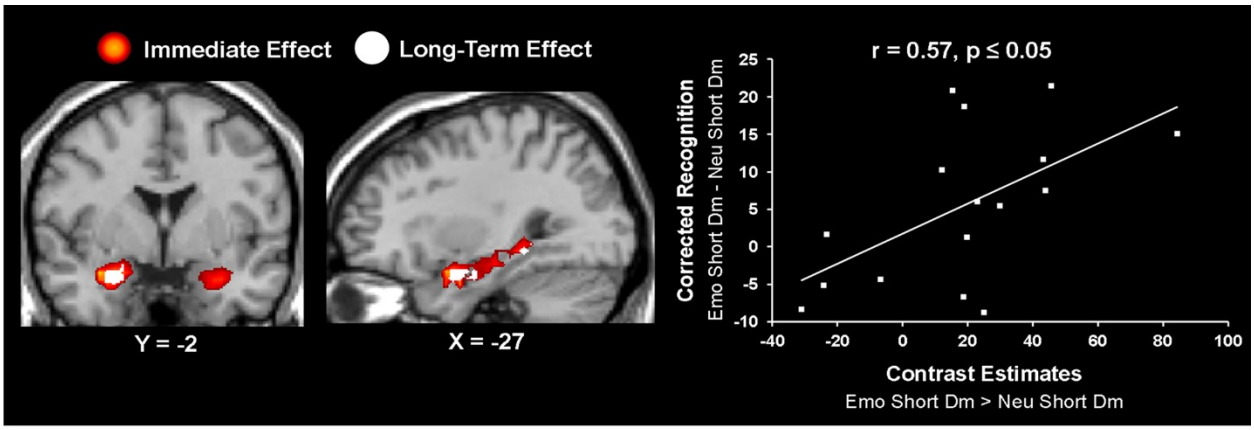

Figure 3-5. Hemispheric Dissociation Linked the Immediate vs. Long-Term Effects of Emotion in the Amygdala and Hippocampus. Left panel shows a coronal view of the AMY, highlighting the lateralization effect showing the bilateral immediate effect of emotion (in red) and the left-lateralized long-term effect of emotion (in white). The middle panel shows a sagittal view of AMY-HC regions illustrating the immediate and long-term effects of emotion The right panel shows a scatterplot illustrating the results from the peak voxel of the correlation calculated on the contrast estimates from the long-term effect of emotion during the short Dur condition and the corresponding behavioral data, as extracted from left AMY (Talairach coordinates: x = -27, y = -4, z = -15). The contrast used for creating the correlation *t*-maps was [(Emo Short Dm vs. Neu Short Dm) ∩ (Emo Short Dm)]. The resulting joint probability for the correlation *t*-map is $p < 0.000125$; see Methods section for details. Emo = Emotional; Neu = Neutral; Dur = Stimulus Duration; Dm = Difference due to memory; AMY = Amygdala; HC = Hippocampus.

CHAPTER 4

THE LONG-TERM IMPACT OF EMOTION ON COGNITION: DISSOCIATING MEMORY PROCESSES INVOLVED IN THE MEMORY-ENHANCING EFFECT OF EMOTION.

Dissociating Retrieval Success from Incidental Encoding Activity during Emotional Memory Retrieval, in the Medial Temporal Lobe

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Investigations examining the impact of emotion on memory have shown emotion enhances memory (Bradley, Greenwald, Petry, & Lang, 1992; Chiu, Dolcos, Gonsalves, & Cohen, 2013; Christianson, 1992), and that this enhancement is associated with increased engagement of emotion (amygdala - AMY) and memory (hippocampus – HC and parahippocampus, PHC) related medial temporal lobe (MTL) regions. This increased engagement is observed during both encoding (Dolcos & Denkova, 2008; Dolcos, Denkova, & Dolcos, 2012; Dolcos, LaBar, & Cabeza, 2004; McGaugh, 2004; Murty, Ritchey, Adcock, & LaBar, 2011) and retrieval (Dolcos, LaBar, & Cabeza, 2005; Kensinger & Schacter, 2005; Sergerie, Lepage, & Armony, 2006; Sharot, Delgado, & Phelps, 2004; Smith, Stephan, Rugg, & Dolan, 2006). While the MTL's role in encoding success operations contributing to the memory-enhancing effect of emotion has been well documented, open questions still remain concerning its role in emotional memory retrieval. One unclear aspect concerns the dissociation between neural activity linked to retrieval success processes from activity associated with encoding processes that occur during retrieval. Due to the nature of recognition memory tasks used to study the neural correlates of memory retrieval, it is unclear whether MTL regions identified as being associated with retrieval processes are unique to retrieval or are common to both the successful retrieval of previously encoded items and incidental encoding processes that occur during retrieval. The present study addresses this issue by using functional magnetic resonance imaging (fMRI) in conjunction with an experimental design that allowed for the dissociation of MTL involvement in retrieval success from incidental encoding success, during the retrieval of emotional memories.

Investigations of MTL activity associated with incidental memory formation during non-emotional memory retrieval (Stark & Okado, 2003) found MTL regions associated with neutral

retrieval success largely overlapped with those involved in the incidental encoding success of lure items. Even though a large amount of overlap was found, specificity within the HC was also found such that areas in the HC were identified as being associated with retrieval success after accounting for incidental encoding during retrieval. However, to our knowledge similar investigations have not been performed during emotional memory retrieval. Therefore, it remains unclear whether or not activity linked to the memory-enhancing effect of emotion identified in MTL-based emotion and memory regions during emotional memory retrieval can be distinguished from activity related to the memory-enhancing effect of emotion associated with the incidental formation of emotional memories during retrieval. Hence, the first goal of the present investigation was to address this issue by identifying MTL activity specifically related to the successful retrieval of emotional memories that does not contribute to incidental encoding during emotional memory retrieval.

Recognition memory tasks involve various aspects of processing, including retrieval operations *per se*, re-encoding/consolidation of retrieved memories, and incidental encoding of new information presented as lures. The focus of the present investigation is to distinguish between MTL areas subserving memory operations that contribute to the successful retrieval of information from MTL areas involved in incidental memory formation during retrieval. It should be noted that in the context of the present investigation we refer to "encoding operations" from a mnemonic not perceptual perspective. The former refer to memory-specific processing that leads to the formation of new memories, whereas the latter refer to general perceptual processing that occurs regardless of subsequent memory effects. Regarding the identification of activity underlying processing that contributes to retrieval success, there are currently two methodological approaches. One compares activity for Old items correctly identified as Old

(Hits) and activity for Old items incorrectly identified as New (Misses), and the other compares activity for Hits and New items correctly identified as New (Correct Rejections, CR).

We defined retrieval success activity as resulting from the comparison between Hits and Misses, because the comparison between Hits and Correct Rejections makes it difficult to distinguish between various aspects of processing during retrieval. For example, if a brain region is involved in both retrieval success *per se* and incidental encoding success during retrieval, then the incidental encoding success activity in response to a lure item that was correctly rejected may equate the retrieval success activity in response to an Old item that was remembered. In this situation a brain region would erroneously show no involvement in retrieval success activity, because it contributes to both aspects of processing. This has previously been shown for the involvement of MTL regions in non-emotional memory retrieval and incidental encoding (Stark & Okado, 2003).

One way to identify incidental encoding success activity, and dissociate it from retrieval success activity, is to use a second subsequent memory task (second retrieval task) and compare brain activity for Misses that are subsequently remembered to Misses that remain forgotten. However, this contrast cannot control for the effects associated with repeated presentation of these items, which may eventually lead to their encoding into memory. Therefore, it is difficult to determine if later memory for Misses that were initially forgotten during the first retrieval task and then remembered during the second retrieval task is due to successful encoding during the first retrieval or due to a repeated exposure effect where the signal for a particular item may finally surpass the criteria necessary for Old responses.

We favor an alternative way of identifying incidental encoding success activity during retrieval and dissociate it from retrieval success activity, while avoiding repeated presentation.

This involves comparison of activity for New items/lures presented during the first retrieval task that are then remembered or forgotten in a subsequent memory task (second retrieval task). In this regard, incidental encoding success activity during retrieval refers to the successful encoding of items presented as lures during the first retrieval task. Using this approach allows for the separation of retrieval success activity, obtained by comparing Hits and Misses, from incidental encoding success activity resulted from the contrast between the remembered lures and forgotten lures (in the second retrieval task).

Previous investigations of the neural mechanisms of emotional memory have pointed to spatial and temporal dissociations. Regarding the former, fMRI investigations have identified an anterior-posterior dissociation in the MTL, with emotional memory involving more anterior regions (AMY and anterior PHC regions) and neutral memory involving more posterior regions (HC and posterior PHC) (Dolcos, et al., 2004; Dougal, Phelps, & Davachi, 2007; Kensinger & Schacter, 2005; Sharot, et al., 2004). Regarding temporal dissociations, event-related potential (ERP) studies have pointed to earlier memory-related processing contributing the memory-enhancing effect of emotion compared to that contributing to non-emotional memory (Dolcos & Cabeza, 2002). Although this finding is consistent with previous research highlighting faster processing of emotional information (Dolcos & Cabeza, 2002; Larson et al., 2006; Mendez-Bertolo et al., 2013), it is uncertain if these timing differences can also be observed in the BOLD response within the MTL during retrieval, given that the temporal resolution offered by fMRI is less than ideal for determining the precise temporal characteristics of cognitive processes. Nevertheless, some information concerning their timing may still be gleaned (Daselaar et al., 2008; Larson, et al., 2006; Schuyler et al., 2012; Siegle, Steinhauer, Thase, Stenger, & Carter, 2002). For example, emotional and neutral retrieval activity may possess similar magnitudes, but

time to peak onset of those magnitudes may differ, thus revealing dissimilarities between the associated neural mechanisms of these processes that would otherwise remain hidden when not considering the time course of the BOLD response. To that end, the second goal of the present investigation was to explore the possibility of differences in the time course of the BOLD response for emotional and neutral retrieval activity in the MTL.

These issues were addressed by using an experimental design in which participants sequentially performed three tasks to identify and compare the neural correlates of retrieval success to those associated with incidental encoding success during retrieval. First, participants performed a perception task that served as the "study phase" for the items used to examine the neural correlates of retrieval. Then, immediately following the perception task, participants performed an episodic memory task that served as the "test phase" for the items used to examine the neural correlates of retrieval as well as the "study phase" for lure items used to identify the neural correlates of encoding during retrieval. Lastly, participants performed another episodic memory task that served as the "test phase" for the lures that were presented during the first episodic memory task. For the current investigation we restricted our analyses to regions within the MTL. This was done for three reasons. First, the MTL engagement in memory processes is among the most systematic findings in the neuroscience literature; hence, we targeted this region due to its reliable involvement in the processes under investigation. Second, while other non-MTL brain regions (e.g., frontal and parietal cortices) are also contributing to the memory-enhancing effect of emotion, their involvement tends to be mediated by the contribution of other processes, such as attention, working memory, and semantic memory (Dolcos, et al., 2012; Shafer & Dolcos, 2012). In contrast, MTL regions are less susceptible to such influences due to their relatively automatic engagement during the encoding and retrieval of emotional memories

(Ritchey, LaBar, & Cabeza, 2011; Shafer & Dolcos, 2012). Third, we primarily sought to build on the existing literature concerning the present research topic, where there was focus only on MTL-based memory regions for non-emotional memories (Stark & Okado, 2003).

Based on the extant evidence we made the following three predictions: Concerning the first main goal and consistent with previous research examining the influence of emotion on memory, we predicted enhanced memory for emotional relative to neutral items, during both memory tasks. Regarding the fMRI findings and based on earlier research for non-emotional memory (Stark & Okado, 2003), we predicted that the memory-enhancing effect of emotion at retrieval would be at least partially accounted for by activity related to memory-enhancing effect of emotion associated with incidental encoding during retrieval. Concerning the second main goal, based on previous findings showing encoding processes associated with the memory-enhancing effect of emotion occurring earlier (Dolcos & Cabeza, 2002) and influencing more anterior MTL regions (Dolcos et al., 2004), we explored the possibility that similar differences could also be identified at retrieval, with emotional retrieval success occurring earlier and in more anterior MTL regions than the neutral retrieval success.

Methods

Participants

Data from a group of 17 healthy young adults [19 - 33 years of age (M = 23.11, SD = 4.01); 10 female; all right-handed] were analyzed for the present investigation. Data from all 17 participants was used to examine the influence of emotion on immediate memory. Data from 10 participants (19 - 33 years of age, M = 24.6, SD = 4.53, 7 female) was used to examine the influence of emotion on delayed memory in order to examine incidental encoding during retrieval. Participants were recruited from the Edmonton City area, provided written informed

consent before participating, and were reimbursed for their participation. The experimental protocol was approved for ethical treatment of the human participants by the Institutional Health Research Board.

Tasks and Stimuli

Each participant performed a perceptual orientation discrimination task and an episodic memory task (EM-1), while brain imaging data were collected using fMRI (Shafer & Dolcos, 2012; Shafer et al., 2012). One-week following the completion of these two tasks, participants also performed a delayed episodic memory task (EM-2) for items that were presented as lures during the immediate episodic memory task (see task diagram illustrated in Figure 1). In the perceptual orientation discrimination task, participants made decisions on the orientation of vertical and horizontal pictures with negative and neutral content. In the memory task immediately following the perception task, participants made decisions about whether emotional and neutral pictures had been presented during the perception task (Old) or they had not seen before (New). In the delayed memory task, performed 5-7 days after the completion of the first two tasks, participants made decisions about whether or not emotional and neutral pictures were presented as lures during the immediate episodic memory task or were New items that had not been seen before. All of the emotional and neutral pictures were selected from the International Affective Pictures System (Lang, Bradley, & Cuthbert, 2008), based on normative arousal and valence ratings and from in-house pictures used in previous studies (Dolcos & McCarthy, 2006; Yamasaki, LaBar, & McCarthy, 2002). For each individual task, valence and arousal scores were significantly different for emotional and neutral pictures. Notably, the arousal and valence scores did not differ across tasks within emotional or neutral picture categories. Since our main goal focused on effects associated with the overall emotional charge, rather than on identifying the relative

contribution of basic emotional dimensions (arousal vs. valence), the present results cannot distinguish between the contribution of these two affective dimensions to the observed effects.

[Figure 1 about here]

Perception task. The stimuli and design of the perception task are identical to those described previously (Shafer, et al., 2012). Briefly, the perception task manipulated the attentional demand necessary to determine the orientation of vertically or horizontally presented pictures that contained emotional (negative), non-emotional (neutral), or no distraction (scrambled). The mean arousal (1 = Lowest/9 = Highest) and valence (1 = Very Negative, 5 = Neutral, 9 = Very Positive) scores for the 224 pictures used during the perception task, respectively, were as follows: 5.9/2.75, for emotional pictures; 3.35/5.05 for neutral pictures. Participants were instructed to determine the orientation of the rectangles, to maintain focus on the orientation task, and to respond as accurately and quickly as possible.

Episodic Memory task 1 (EM-1). The stimuli and design of the immediate episodic memory task are identical to those described previously (Shafer & Dolcos, 2012). Briefly, EM-1 was a surprise memory task for items that were presented as distracters during the perception task. This task consisted of 160 pictures, which were a sub-set of the 224 pictures that were presented in the initial perception task. These Old images were pseudo-randomized with 80 New pictures (40 emotional, 40 neutral) that were selected on normative arousal and valence scores and semantic content from the same picture databases used for the perception task. The average normative arousal and valence scores for Old and New emotional and neutral pictures for the first episodic memory task, respectively, were as follows: 5.93/2.63 for emotional Old pictures; 5.95/2.66 for emotional New pictures; 3.41/5.04, for neutral Old pictures; and 3.41/5.02 for neutral New pictures. To ensure a minimum retention interval for the memory-enhancing effect of emotion to

occur, a minimum delay of 20 minutes between the initial encoding and first retrieval task was imposed (Kleinsmith & Kaplan, 1963). Participants were randomly assigned one of two run orders which allowed for a similar delay period between encoding and retrieval. This was essential to the overall design of the paradigm as Old stimuli in the first episodic memory task were pseudo-randomized based on when they appeared in the perception task. This resulted in a delay of approximately 40 min between the encoding and retrieval of a stimulus. For example, if a picture was presented in the first run of the perception task, then it would be presented in either the first or second run of the recognition task. Likewise, if a stimulus was presented in the last run of the perception task then it was presented in the second to last or last run of the recognition task.

Episodic Memory task 2 (EM-2). Approximately one-week later (Range = 5 – 7 days; Mean = 6.8) following the completion of the perception and EM-1 tasks participants performed an episodic memory task for items that were presented as lures during EM-1. The 80 Old pictures that served as lures during EM-1 were pseudo-randomized with 40 (20 emotional, 20 neutral) *New* lure pictures. Old and New pictures did not statistically differ in normative arousal and valence, other than between the emotional and neutral pictures – negative pictures were significantly more negative and arousing than neutral pictures. The average normative arousal and valence scores for Old and New emotional and neutral pictures for the second episodic memory task, respectively, were as follows: 5.95/2.66 for emotional Old pictures; 5.91/2.46 for emotional New pictures; 3.41/5.02, for neutral Old pictures; and 3.52/5.00 for neutral New pictures.

Experimental Procedures

After the first experimental session (consisting of the perception and EM-1 tasks) participants were asked to return to the lab for further testing in one-week. The procedure for EM-1 is identical to that described in Shafer & Dolcos, 2012. Approximately one-week later 14 participants returned and completed EM-2 outside of the scanner. The test included a total of 120 pictures (80 Old, 40 New) distributed across 5 runs (24 pictures/run). To avoid mood induction, trials were pseudo-randomized such that no more than two consecutive trials of the same valence type occurred. As with EM-1, each picture was displayed for 2 sec during which participants had to indicate with a button press whether the picture was Old, presented during EM-1 or New, not presented in EM-1. Immediately following the 2 sec response window a confidence rating screen was presented for 2 sec asking participants to indicate the level of confidence (LOC) for their decision on a three-point Likert scale (1 = lowest, 3 = highest). Each trial was followed by a jittered fixation interval drawn from an exponential distribution with a median of 6 sec (Range = 4 - 12 sec). Similar to EM-1, participants were not informed of the EM-2 task. During both memory tasks participants were instructed to respond accurately and quickly, and that if they were unsure if a picture was Old or New to provide their best guess and indicate that their decision was uncertain by assigning that trial a low confidence rating.

Imaging Protocol

MRI data were collected on a 1.5-T Siemens Sonata scanner. After the sagittal localizer and the 3-D MPRAGE anatomical images (TR = 1600 msec; TE = 3.82 msec; FOV = 256 x 256 mm; number of slices = 112, voxel size = 1 mm^3), EPI functional volumes allowing for full brain coverage were acquired axially (TR = 2000 msec; TE = 40 msec; FOV = 256 x 256 mm; number of slices/volume = 28, voxel size = 4 x 4 x 4 mm).

Behavioral Analyses

Responses in EM-1 and EM-2 tasks were classified into one of four categories (Hits – Old pictures correctly identified as Old; Misses – Old pictures incorrectly identified as New; CRs – New pictures correctly identified as New; False Alarms (FAs) – New pictures incorrectly identified as Old), as derived from signal detection theory (Macmillan & Creelman, 1991). These categories were used to calculate corrected recognition (% Hits - % FAs) scores. Since the main goal of the present investigation was to distinguish between the neural correlates of retrieval success and incidental encoding success during retrieval, all trials from the perception task were included in the data analysis for EM-1 (i.e., regardless of whether they were correct or incorrect). Previous analyses of this data set focused on brain imaging data acquired during the perception task and results focused on emotional distraction and encoding success for correct trials were published elsewhere (Shafer & Dolcos, 2012; Shafer, et al., 2012). To maximize the difference in the MTL response during retrieval to remembered and forgotten items, only items that were given a LOC of 3 were included in the data analyses for both EM-1 and EM-2 tasks (Daselaar, Fleck, & Cabeza, 2006; Kleinsmith & Kaplan, 1963; Yonelinas, 2001). To assess the influence of emotion on memory performance, emotional and neutral corrected recognition scores were entered into a paired samples *t*-test. This was done separately for EM-1 and EM-2. To determine if differences in the delay period between EM-1 and EM-2 affected memory performance corrected recognition scores across the two tasks were examined using repeated measures analyses of variance (ANOVA) for the 10 participants who had both EM-1 and EM-2 data. Task (EM-1, EM-2), Valence (Emo, Neu), and Memory (Hit, Miss) were within-subjects variables. Post-hoc comparisons were performed where appropriate and Bonferroni corrected.

fMRI Analyses

Statistical analyses were preceded by the following preprocessing steps (performed with SPM2 – Statistical Parametric Mapping): TR alignment, motion correction, normalization, and smoothing (8 mm kernel). For the data analysis, we used in-house custom MATLAB scripts involving both whole-brain voxel-wise and region-of-interest (ROI) analyses to compare brain activity associated with conditions of interest. For subject-level analyses, the fMRI signal was selectively averaged for each participant as a function of trial type (i.e., emotional hits, emotional misses, neutral hits, neutral misses, remembered emotional lures, forgotten emotional lures, remembered neutral lures, forgotten neutral lures) and time point (or TR; one pre- and 8 post-stimulus-onset) using custom MATLAB scripts. Pair-wise *t* statistics for the contrasts of interest were calculated for each subject; no assumption was made about the shape of the hemodynamic response function (Dolcos, Diaz-Granados, Wang, & McCarthy, 2008; Dolcos & McCarthy, 2006; Morey et al., 2009). Individual analyses produced whole-brain activation *t* maps for each condition, contrast of interest, and TR/time point (TP). The outputs of the subject-level analyses were used as inputs for the second-level, random-effects within-group analyses.

Region of Interest (ROI) Analyses

Identification of Brain Activity Linked to Retrieval Success and the Incidental Encoding Success of Lure Items. Of the fourteen participants that completed EM-2, only 10 participants met the criteria for inclusion when examining the number of trials per condition for LOC 3 responses. Criteria for inclusion required that each participant have at least five (Huettel & McCarthy, 2001) good trials (raw MR signal > = 300 MR unit) per trial type, associated with high level of confidence (LOC 3) ratings. Thus, imaging data analyses assessing the neural correlates of retrieval success were performed on data from 17 participants, while imaging data analyses

assessing the neural correlates incidental encoding success were performed on data from 10 participants. To identify MTL activity linked to the memory-enhancing effect of emotion, analyses directly comparing brain activity between emotional and neutral retrieval success/encoding success (i.e., Hits – Misses) were performed on trials where behavioral differences were observed and where memory strength is the strongest (i.e., LOC3 trials). Brain regions associated with emotional (Emotional Hits > Misses) and neutral (Neutral Hits > Misses) memory were separately identified for each time point. These contrasts for emotional and neutral retrieval success/encoding success were then entered into a paired samples *t*-test which was then inclusively masked by the main effect of emotional retrieval success/encoding success (Emotional Hits > Misses). This procedure allowed identification of MTL regions where activity for emotional retrieval success/encoding success was greater than for neutral retrieval success/encoding success, for each time point [i.e., ((Emotional Hits – Misses) vs. (Neutral Hits – Misses)) ∩ (Emotional Hits – Misses)]. The inclusive masking of the analysis (or conjunction analyses) identified greater retrieval success for emotional than for neutral pictures [i.e., (Emotional Hits > Misses) > (Neutral Hits > Misses)]. This was necessary to ensure that the interaction difference occurred in regions also showing significant retrieval success activity for the emotional pictures (Emotional Hits > Misses). This is a more conservative procedure in identifying differences between retrieval success activity for emotional and neutral material because it eliminates areas where such differences could be driven by the absence of retrieval success activity for emotional stimuli (e.g., if activity for Emotional Hits is not significantly greater than for Emotional Misses) coupled with effects going in opposite direction for the neutral pictures (Neutral Misses > Neutral Hits). To identify MTL regions where the response for neutral memory was greater than the response to emotional memory contrasts for neutral

retrieval success/encoding success were entered into a paired samples *t*-test which was then inclusively masked by the main effect of neutral retrieval success/encoding success [i.e., ((Neutral Hits – Misses) vs. (Emotional Hits – Misses)) ∩ (Neutral Hits – Misses)]. Conjunction analyses involved masking procedures performed in MATLAB using the logical function AND. Thus, only voxels that met the threshold criteria in each of the contributing *t* maps survived the masking procedure. This procedure is consistent with the conjunction null hypothesis testing (Nichols, Brett, Andersson, Wager, & Poline, 2005). In addition, areas of activation were corrected for multiple comparisons in two ways. We applied two levels of false discovery rate (FDR) corrections - one corresponding to a p-value of 0.05 (Genovese, Lazar, & Nichols, 2002) for each anatomical ROI, and the other corresponding to a p-value of 0.05 for each functional cluster within anatomically restricted ROIs (i.e., restricted to the anatomical boundaries of the MTL ROIs) – see Tables 1 and 2. The present procedure involving FDR corrections and conjunction analyses, along with the report of both corrected and uncorrected statistical values offer a good balance between the cost of potential Type I and II errors (Lieberman & Cunningham, 2009).The greatest effect in MTL regions for emotional and neutral retrieval success/encoding success occurred from time points 5 - 7 (6 - 10 sec after stimulus onset). MTL activity for these time points was isolated using the Automated Anatomical Labeling atlas (AAL, Tzourio-Mazoyer et al., 2002) in SPM for the HC and PHC. These were used in conjunction with an in-house AMY mask (Dolcos, et al., 2004; Moore et al., In Press) which corrected for large discrepancies in the AAL AMY mask.

Dissociating Retrieval Processes Associated with the Memory-Enhancing Effect of Emotion. MTL activity observed across time points of greatest activity (time points 5-7), as identified in the individual analyses for incidental encoding success was merged in MATLAB using the

logical function OR. This was done separately for emotional and neutral items to identify and collapse all significant areas of activation for each of the peak time points. For example, the clusters of activation identified in the MTL for emotional incidental encoding success (Emotional Lures Remembered - Forgotten) at time points 5, 6, and 7 were combined into one t-map representing MTL activity for emotional incidental encoding success and for the memory-enhancing effect of emotion incidental encoding success [((Emotional Lures Remembered - Forgotten) vs. (Neutral Lures Remembered – Forgotten)) ∩ (Emotional Lures Remembered - Forgotten)]. This same process was applied to *t* maps for neutral encoding success and neutral > emotional encoding success. Due to the low number of participants contributing to the analyses identifying incidental encoding success activity during retrieval, we implemented the incidental encoding success results as binary maps to identify areas showing retrieval success activity that have no contribution to incidental encoding success activity during retrieval. Specifically, we made the group *t*-maps identified by the steps mentioned above for emotional, neutral, emotional > neutral, and neutral > emotional incidental encoding success into binary masks. Specifically, voxels were assigned a value of 1 if p-values were less than or equal to 0.05. All other voxels within the ROIs not meeting this criterion were given a value of zero. For each ROI, *t*-maps corresponding to emotional, neutral, emotional > neutral, and neutral > emotional retrieval success activity were then exclusively masked with this binary mask [e.g., (Emotional Hits > Misses) ~ (Emotional Lure Hits > Lure mMisses), (Neutral Hits > Misses) ~ (Neutral Lure Hits > Lure Misses)], and regions surviving these masking procedures were identified (see Tables 1 and 2). MTL activity for emotional, neutral, emotional > neutral, and neutral > emotional retrieval success t-maps after exclusively masking for activity associated with incidental encoding success

was isolated using the AAL atlas in SPM for the HC and PHC. These were used in conjunction with an in-house AMY mask (Dolcos, et al., 2004; Moore, et al., In Press).

Exploratory Analysis to Investigate Possible Temporal and Spatial Dissociations between Emotional and Neutral Retrieval Success. After exclusively masking by incidental encoding success activity during retrieval, functional ROIs from within region clusters for emotional greater than neutral retrieval success, and neutral greater than emotional retrieval success (e.g., right anterior PHC and right posterior PHC, respectively) were used to extract the fMRI signal for each participant, for each condition, and time point. These data were then entered into a repeated measures analyses of variance (ANOVAs) assessing Memory (Hits, Misses), Valence (Emotional, Neutral), and Time Point (5, 6, and 7). A significant three-way interaction in a region was further investigated at each time point for a Memory by Valence interaction. Follow-up post-hoc comparisons were performed where appropriate and Bonferroni corrected.

Results

Behavioral Results

Increased Memory for Emotional Pictures. To maximize the difference in response to remembered and forgotten items in the brain imaging data, only trials that were given the highest level of confidence (LOC 3) were used for analyses (Daselaar, et al., 2006; Kleinsmith & Kaplan, 1963; Yonelinas, 2001). Analyses of corrected recognition scores for LOC 3 trials for EM-1 showed that emotional pictures (M = 0.23, SE = 0.03) were better remembered than neutral picture (M = 0.17, SE = 0.04), [$t(16) = 1.85$, $p = 0.04$, one-tailed]. Mean hit and false alarm rates for LOC 3 trials in the first episodic memory task for emotional/neutral pictures were as follows: 0.56 (SD = 0.13)/0.37 (SD = 0.18) and 0.33 (SD = 0.14)/0.19 (SD = 0.11), respectively. Similarly, analyses of corrected recognition scores for LOC 3 trials for EM-2

showed that memory for emotional lures (M = 0.19, SE = 0.05) was better than memory for neutral lures (M = 0.04, SE = 0.04), [t(9) = 4.12, p = 0.001]. For the second episodic memory task mean hit and false alarm rates for emotional/neutral pictures were: 0.43 (SD = 0.12)/0.23 (SD = 0.11) and 0.24 (SD = 0.14)/0.19 (SD = 0.1), respectively. These analyses identified greater memory for emotional than neutral pictures in both EM tasks, with a numerically greater emotion effect following longer delay (Dolcos, et al., 2005; Ritchey, Dolcos, & Cabeza, 2008) – see Figure 2A. To investigate whether this interaction between emotional memory and EM task was significant a repeated measures ANOVA with the variables Task, Valence, and Memory was performed on the 10 participants who met the LOC 3 criterion for EM-2. The impact of emotion on memory was found to increase by 46% from EM-1 to EM-2. However, this increase across tasks was not statistically significant [F(1,9) = 1.44, p = 0.26]. Interestingly though, and consistent with research showing emotional memories persist better over time compared to neutral memory (Dolcos, et al., 2005; Ritchey, 2008; Ritchey, et al., 2008), this apparent change in the impact of emotion on memory across tasks was not due to an increase in emotional memory *per se* [t(9) = 0.82, p = 0.43], but because of a decrease in the neutral memory in the second episodic memory task [t(9) = 2.37, p = 0.04] – see Figure 2B.

[Insert Figure 2 about here]

fMRI Results

Dissociating Retrieval Processes Linked to the Memory-Enhancing Effect of Emotion. To examine MTL activity associated with the memory-enhancing effect of emotion at retrieval we first contrasted activity for emotional remembered and forgotten items, and neutral remembered and forgotten items. Increased activity throughout the MTL was identified in response to emotional and neutral memory (see Table 1). Next, to examine the memory-enhancing effect of

emotion at retrieval, we contrasted activity for emotional and neutral memory [(Emo Hits > Misses) > (Neu Hits > Misses)]. Replicating previous findings of the involvement of MTL regions in the retrieval of emotional items (Dolcos, et al., 2005), emotional compared to neutral retrieval success resulted in greater activity in bilateral AMY, HC, and PHC (see Table 2). When examining retrieval-related activity without accounting for activity related to incidental encoding success during retrieval, three clusters of activity were identified in the AMY. A left hemisphere cluster extended through the entire amygdala and two right hemisphere clusters, one located laterally and the other medially. Two clusters of activity were identified in the HC. A right hemisphere cluster localized more anteriorly and a left hemisphere cluster that extended the entire length of the HC and contained an anterior, middle, and posterior peak. The PHC contained two clusters of activity in response to emotional greater than neutral retrieval success, one left and one right. Both clusters extended throughout the PHC and contained three peaks, an anterior, middle, and posterior peak.

[Insert Table 1 about here]

To investigate MTL activity dissociating retrieval success from incidental encoding successes during retrieval linked to the memory-enhancing effect of emotion we exclusively masked retrieval activity by incidental encoding activity [((Emo Hits > Misses) > (Neu Hits > Misses)) ~ ((Emo Lures Remembered > Forgotten) > (Neu Lures Remembered > Forgotten))]. MTL retrieval success activity related to the memory-enhancing effect of emotion that survived exclusive masking by incidental encoding success activity related to the memory-enhancing effect of emotion was identified in the left AMY, bilateral HC and PHC (see Table 2 and Figure 3A). For AMY, the two right hemisphere clusters identified for retrieval success also contributed to incidental encoding success. For the HC and PHC, partial activity within each of the clusters

identified for retrieval success also contributed incidental encoding success during retrieval. However, all of the cluster peaks identified for retrieval success survived the exclusive masking procedure.

[Insert Table 2 and Figure 3 about here]

In addition, investigation of MTL areas with greater sensitivity to neutral than to emotional retrieval [(Neu Hits > Misses) > (Emo Hits > Misses)], identified the right posterior HC and PHC. To determine whether this retrieval-related activity contributed to the incidental encoding of neutral lure items, we exclusively masked retrieval-related by incidental encoding-related activity [((Neu Hits > Misses) > (Emo Hits > Misses)) ~ ((Neu Lures Remembered > Forgotten) > (Emo Lures Remembered > Forgotten))]

Activity surviving the exclusive masking procedure was located in the right posterior PHC (see Table 2 and Figure 3B and C). Right posterior HC activity was found to contribute to both retrieval and incidental encoding success of neutral lure items during retrieval.

Exploratory Analysis Investigating Possible Temporal and Spatial Dissociations between Emotional and Neutral Retrieval Success. To examine differences in the temporal dynamics for retrieval processes linked to the enhancement of emotional versus neutral memory, and vice-versa (as observed in Table 2), we investigated changes in retrieval success activity over the peak time points of activation (time points 5-7). Sub-regions of the MTL sensitive to the enhancement of emotional or neutral retrieval success, that survived exclusive masking by encoding success activity during retrieval (see Table 2), showed earlier modulation for the enhancing effect of emotion (left AMY, bilateral HC and PHC) and later modulation for enhancement of neutral memory (right posterior PHC) - see Supplemental Material. Regarding spatial dissociation, although greater emotional than neutral retrieval success activity was identified in AMY, HC,

and PHG, regions showing greater neutral than emotional retrieval success were restricted to more posterior regions of the MTL (PHC) (see Table 2).

Discussion

The present study used a novel experimental paradigm to dissociate between retrieval success activity and incidental encoding success during emotional retrieval in the MTL. Two novel findings regarding the neural correlates of emotional retrieval were identified. First, greater emotional retrieval success was identified bilaterally in AMY, HC and PHC. However, AMY was most impacted when accounting for encoding success activity, as only retrieval success activity in the left but not right AMY was dissociated from encoding success activity during retrieval, whereas the portions of HC and PHC showing greater emotional retrieval success were largely uninvolved in encoding success. Second, an earlier and more anteriorly spread response (in left AMY and bilateral HC and PHC) was linked to greater emotional retrieval success, whereas a later and more posteriorly localized response (in right posterior PHC) was linked to greater neutral retrieval success. These findings are discussed in turn below.

Dissociating Retrieval Processes Linked to the Memory-Enhancing Effect of Emotion. Memory performance for emotional relative to neutral items for EM-1 and EM-2 replicates findings from a large body of extant research examining item-based emotional memory (for review see - Chiu, et al., 2013; Dolcos, et al., 2012). Although the impact of emotion on memory for EM-1 is numerically weaker than what was found for EM-2, specific aspects of present study's design can account for this difference. First, EM-1 tested memory for items that were presented as task-irrelevant distracters during initial encoding. Thus, divided attentional resources between processing these task-irrelevant items and those required for performing the main perceptual task most likely resulted in a decrease in overall memory performance

(Uncapher & Rugg, 2005). Furthermore, the emotional distracter items that served as memoranda in EM-1 were most difficult to ignore during the perception task. As a result, participants may have engaged mechanisms to minimize their influence on the perception task more than those required for performing the perception task in the presence of neutral distraction. Hence, increased engagement of these mechanisms might have also contributed to the decreased impact of emotion on memory, compared to EM-2. Second, although expected to be effective (Dolcos, et al., 2004; Kleinsmith & Kaplan, 1963), our short retention interval (~40 minutes) between encoding and retrieval of a single item also made a difference compared to the longer retention interval for EM-2 (Dolcos, LaBar, & Cabeza, 2005; Ritchey, Dolcos, & Cabeza, 2008). Considering these aspects of the present design, the behavioral effect observed in EM-1 highlights the robustness of emotion's impact on memory, as it was present in conditions where the memoranda were task-irrelevant during initial encoding and when the retention interval was short.

Our result showing the persistence of emotional memory over time is also consistent with a number of earlier behavioral and neuroimaging studies (Anderson, Yamaguchi, Grabski, & Lacka, 2006; Dolcos, et al., 2005; Kleinsmith & Kaplan, 1963; Ritchey, et al., 2008; Sharot & Phelps, 2004; Sharot & Yonelinas, 2008). Enhanced memory performance for emotional relative to neutral items was associated with increased engagement of all three main regions of the MTL (AMY, HC, and PHC) during retrieval. The emotional enhancement of memory linked to increased engagement of these regions during retrieval replicates previous neuroimaging studies of emotional retrieval (Dolcos, et al., 2005; Kensinger & Schacter, 2005; Sergerie, et al., 2006; Sharot, et al., 2004; Smith, et al., 2006).

The first novel finding of the present study involved the identification of MTL sub-regions that survived exclusive masking by incidental encoding success processes co-occurring during retrieval. When considering this finding in the context of the various aspects of processing that occur during retrieval (including retrieval operations *per se*, re-encoding/consolidation of retrieved memories, and incidental encoding of new information presented as lures), the current investigation offers insight into MTL sub-regions that may distinguish between retrieval operations and other memory operations occurring during retrieval (specifically, the encoding of new information presented during retrieval). As mentioned, encoding operations can refer to general perceptual processing or mnemonic processing that leads to the formation of new memories. As implemented here, one way of distinguishing between incidental encoding activity during retrieval from activity specifically linked to retrieval, while controlling for repeated exposure effects is to 1) define retrieval success as the difference in activity between Hits and Misses, and 2) compare activity for remembered vs. forgotten New items that were presented as lures during retrieval. This approach allows for the comparison of brain activity related to memory operations involved in successful retrieval of Old items, to brain activity related to memory operations involved in successful encoding of New items during retrieval. Using this approach, we found greater emotional retrieval success was identified bilaterally in AMY, HC and PHC. However, AMY was most impacted when accounting for encoding success activity, as only retrieval success activity in the left but not right AMY was dissociated from encoding success activity during retrieval, whereas the portions of HC and PHC showing greater emotional retrieval success were largely uninvolved in encoding success.

Retrieval processes have long been thought to involve the reactivation of activity during encoding (Johnson & Rugg, 2007; Nyberg, Habib, McIntosh, & Tulving, 2000) and neuroimaging research has provided much support for this idea, with numerous studies showing that successful memory performance is associated with encoding-retrieval overlap in activations (Johnson, McDuff, Rugg, & Norman, 2009; Johnson & Rugg, 2007; Nyberg, et al., 2000; Ritchey, Wing, Labar, & Cabeza, 2012; Wheeler, Petersen, & Buckner, 2000). Moreover, emotional arousal has been shown to strengthen the relationship between memory performance and encoding-retrieval overlaps (Ritchey, et al., 2012). Thus, it is reasonable to expect that successful retrieval of emotional memories involves the engagement of similar mechanisms to those involved during successful encoding. However, the dissociation in MTL mechanisms during retrieval linked to retrieval success from those linked to encoding success demonstrate it is possible to clarify the MTL's involvement in different aspects of retrieval during recognition memory tasks. Open questions remain regarding the mechanisms involved in the re-encoding/consolidation of emotional memories during retrieval (Nader & Einarsson, 2010) in the human brain.

Exploratory Analysis Investigating Possible Temporal and Spatial Dissociations between Emotional and Neutral Retrieval Success. The second novel finding from the current study identified MTL regions where differences in the temporal dynamics of the BOLD response were found with an earlier response to emotional enhancement of memory (left AMY, bilateral HC and PHC) and a later response to neutral enhancement of memory (right posterior PHC). This finding provides support for earlier research showing the neural mechanisms subserving encoding of emotional memories are more quickly engaged than for neutral information (Dolcos & Cabeza, 2002; Larson, et al., 2006; Mendez-Bertolo, et al., 2013). Importantly, the current

data extend these findings by showing that similar differences in timing are also present at retrieval. It is well known that emotion enhances the magnitude of early and late neural markers of stimulus processing, as shown by ERP studies (Olofsson, Nordin, Sequeira, & Polich, 2008), although shifts in the latency of ERP components indexing sensory and cognitive processes influenced by emotion are not commonly found (e.g., though this may be the result of event-related averaging vs. single-trial variability for ERP data). Also, negative emotions can produce faster responses of the oculomotor system resulting in quicker localization of threat (Bannerman, Hibbard, Chalmers, & Sahraie, 2012; Bannerman, Milders, de Gelder, & Sahraie, 2009). Interestingly and as also shown in the present results, fMRI studies of emotion processing have begun to show differences in the temporal dynamics of the BOLD response between conditions. These differences account for variance that would otherwise remain unexplained. While interesting, these results should be treated with caution given the relatively poor temporal resolution of fMRI. More light will be shed on this topic as neuroimaging techniques advance to allow for the direct comparison and/or integration of more superior temporal techniques with more superior spatial techniques (e.g., simultaneous recordings of EEG and fMRI).

We also identified activation within the MTL showing greater neutral compared to emotional retrieval success. This activation was restricted to posterior HC and PHC regions. Only one right posterior PHC cluster survived exclusive masking by encoding success activity. Posterior MTL involvement in neutral greater than emotional retrieval success is consistent with previous research showing an anterior (emotional) – posterior (neutral) dissociation in the MTL during emotional memory encoding (Dolcos, et al., 2004; Dougal, et al., 2007) and retrieval (Kensinger & Schacter, 2005; Sharot, et al., 2004). The reasons for this anterior-posterior dissociation remain unknown, but it has been suggested that this dissociation may be linked to

the location relative to the AMY, with the anterior memory-related MTL regions being closer to the AMY and thus more involved in emotional memory due to rich interconnections between the AMY and anterior HC/PHC. The involvement of anterior MTL during emotional memory retrieval is consistent with the modulation hypothesis (McGaugh, 2004) of emotional memory encoding and consolidation, and with evidence from previous studies of emotional retrieval. The modulation hypothesis suggests that AMY exerts neuromodulatory influences on other brain regions (e.g., the MTL memory system) involved in the memory formation. Our result showing more anterior MTL engagement during emotional memory retrieval is consistent with earlier reports on emotional retrieval (Dolcos, et al., 2005; Kensinger & Schacter, 2005; Sergerie, Lepage, & Armony, 2006; Smith, Stephan, Rugg, & Dolan, 2006), where the functional interactions supported by the modulation hypothesis for encoding and consolidation are extended to retrieval (LaBar & Cabeza, 2006). While the neurobiological mechanisms underlying AMY-MTL memory system functional interactions during retrieval remain largely unclear, they have begun to be elucidated by psychopharmacological and animal studies. For instance, research showing the β-adernergic blockade of the memory-enhancing effect of emotion during retrieval (Kroes, Strange, & Dolan, 2010) and increased synchronization between AMY and HC during fear retrieval (Seidenbecher, Laxmi, Stork, & Pape, 2003) suggest the neuromodulatory role of the AMY in emotional memory is similar for encoding, consolidation, and retrieval. This is consistent with the current findings showing overlap between retrieval success and encoding success activity during retrieval. However, and as shown here, research also suggest certain aspects of the processes occurring during retrieval can be dissociated (Stark & Okado, 2003), which is also consistent with evidence from animal research (Nader & Einarsson, 2010). On the other hand, posterior HC/PHC regions due to their more remote location from the AMY may not

be as susceptible to its modulatory influences, and hence their involvement in neutral memory is not "overshadowed" by emotion's influence. Instead, these areas are closer to regions associated with visual processing, and thus are perhaps more involved in item processing that engages the ventral visual stream (Dolcos, et al., 2004; Ungerleider, 1995). Although it is interesting to note the current findings show some posterior HC and PHC involvement for the memory-enhancing effect of emotion, the majority of MTL regions identified for this analysis were more anteriorly located, whereas memory enhancement for neutral items was restricted to posterior regions. Future research is needed to clarify the causes of this dissociation.

Caveats. A limitation of the present study is the number of participants contributing to the incidental encoding success analyses. Equal numbers of participants contributing to both retrieval success and encoding success analyses would have been ideal in providing increased specificity when dissociating MTL activity linked to different memory processes during retrieval. Therefore, although the present investigation allowed for identification of areas within the MTL specifically contributing to retrieval success and dissociating from those contributing to incidental encoding success during retrieval, the latter findings should be treated with caution. A high degree of specificity within the MTL in the current study is also limited due to data acquisition and processing parameters. Anatomical specificity is impeded when examining small areas of neural tissue using 4 mm isotropic voxels for data acquisition along with normalization and smoothing kernel of 8 mm for data processing, although these parameters are not unusual for fMRI studies. Future studies using higher spatial resolution and minimal preprocessing will allow for more precise specificity when examining this issue in the MTL. Another limitation of the current study is the difference in delay between encoding and retrieval for EM-1 and EM-2. In EM-1 there were approximately 40 minutes separating the encoding and retrieval of an item,

whereas in EM-2 there was approximately one week separating encoding and retrieval. This difference in delay could have resulted in a shift in retrieval processes that were used during the memory tasks (e.g., from recollection-based for EM-1 to familiarity-based for EM-2). Thus, it is possible that the current findings could be influenced by differences in the retrieval processes implemented across the two memory retrieval tasks. On the other hand, previous research suggests that recollection-based retrieval processes are associated with the highest LOC (Daselaar, et al., 2006). Since we selected only trials with the highest LOC ratings for analysis in both memory tasks there is increased likelihood that memory for these trials is recollection-based in both memory tasks. Moreover, extant research on emotional memory shows that the enhancing effect of emotion results from recollection rather than familiarity-based memory processes (Dew, Ritchey, LaBar, & Cabeza, 2014; Dolcos, et al., 2005). Examination of the relationship between the engagement of certain retrieval mechanisms for items tested during retrieval (e.g., recollection and familiarity) and those engaged for items incidentally encoded during retrieval, linked to the retention interval, is an open question for future research.

CONCLUSIONS

In summary, the present study yielded two novel findings pertaining to the neural mechanisms of emotional memory retrieval. First, the study distinguished between MTL retrieval success and incidental encoding success activity linked to the memory-enhancing effect of emotion during retrieval. Greater emotional retrieval success was identified bilaterally in AMY, HC and PHC. However, AMY was most impacted when accounting for encoding success activity, as only retrieval success activity in the left but not right AMY was dissociated from encoding success activity during retrieval, whereas the portions of HC and PHC showing greater emotional retrieval success were largely uninvolved in encoding success. This finding demonstrates that

MTL activity during retrieval can be dissociated and linked to different memory operations during emotional retrieval. Second, MTL sub-regions were identified as showing different temporal and spatial dissociations in the BOLD response for the memory enhancement of emotional and neutral items. An earlier and more anteriorly spread response (in left AMY and bilateral HC and PHC) was linked to greater emotional retrieval success, whereas a later and more posteriorly localized response (in right posterior PHC) was linked to greater neutral retrieval success. Taken together, these results shed light on the neural mechanisms of emotional memory retrieval in healthy behavior and are important for understanding maladaptive alterations in the processes subserving emotional memory found in populations with affective disorders (Dolcos, 2013; Hayes et al., 2011; Whalley, Rugg, Smith, Dolan, & Brewin, 2009).

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Table 4-1: MTL regions engaged in emotional and neutral retrieval success. The table identifies MTL regions where emotional and neutral RS are significant. The displayed *t* values correspond to the peak voxel for each time point after stimulus onset (where the HDR response was maximal), and represents a significant difference in MR signal between remembered and forgotten items. Emotional RS = (Emotional Hits – Misses) and Neutral RS = (Neutral Hits – Misses). *regions surviving exclusive masking by incidental encoding. ¶region also surviving FDR-anatomical ROI correction. MTL, medial temporal lobe; AMY, amygdala; HC, hippocampus; PHC, parahippocampus; L, left; R, right; RS, retrieval success; HDR, hemodynamic response; MR, magnetic resonance; Cluster Cor., False Discovery Rate-cluster correction

MTL Regions	Hemisphere	Talairach coordinates			*t* values **Cluster Corrected**	Cluster Size	Time (Sec)
		x	*y*	*z*			
Emotional RS							
AMY	L	-19	0	-14	**6.17¶***	62	6
		-30	-8	-11	**5.06¶***		6
		-23	-8	-11	**4.58¶***	5	8
		-30	8	-17	**3.57**	24	8
		-19	4	-14	**2.75***		8
	R	29	4	-13	**5.5¶**	46	6
		21	4	-17	**4.63¶**		6
		14	0	-10	**4.31¶**		6
		25	4	-17	**3.11**	15	8
HC	L	-23	-23	-9	**5.38¶***	69	6
		-34	-11	-12	**5.07¶***		6
		-19	-11	-12	**3.92¶***		6

		-30	-11	-15	**4.62***	59	8
		-19	-15	-12	**3.54**		8
		-16	-27	-6	**2.73**		8
		-30	-11	-15	**2.69***	8	10
	R	29	-12	-7	**3.81¶**	69	6
		18	-4	-17	**3.35¶**		6
		21	-27	-5	**3.26¶**		6
		32	-20	-8	**3.35***	10	8
PHC	L	-19	0	-18	**6.18¶***	70	6
		-23	-22	-20	**5.33¶***		6
		-16	-35	-6	**2.56¶**		6
		-16	4	-14	**4.08***		8
		-31	-34	-10	**3.85**		8
		-27	-18	-20	**3.3***		8
		-19	-27	-9	**2.69***		8
	R	14	-3	-21	**3.66¶**	18	6
		14	4	-13	**3.5¶***		6
		25	-31	-9	**3.51¶***	22	6
Neutral RS							
AMY	L	-23	-1	-7	**2.51***	27	6
		-23	8	-21	**2.41***		6
		-19	0	-14	**2.17**		6
		-16	-8	-11	**3.74***	22	8

		-27	0	-14	**2.49***		8
		-19	4	-14	**1.89***		8
		-16	-4	-11	**3.05***	35	10
		-27	-4	-15	**2.8***		10
		-30	1	-21	**2.69***		10
	R	18	-1	-6	**2.84***	15	6
		21	0	-13	**2.18***	10	8
HC	L	-31	-20	-5	**2.92**	5	6
		-30	-15	-12	**4.07***	42	8
		-27	-11	-12	**3.75***	22	10
		-30	-3	-18	**3.09**		10
	R	14	-35	1	**3.06***	16	6
		21	-24	-5	**2.17**		6
		25	-39	1	**2.56**	11	8
		14	-31	-2	**2.27**		8
		18	-12	-11	**2.43***	6	8
		21	-19	-12	**1.97***		8
		32	-15	-11	1.96*	6	8
		32	-23	-8	1.86*		8
		21	-31	-2	**2.48**	7	10
		21	-39	1	**2.46**		10
		32	-12	-11	**2.26**	7	10
PHC	L	-16	4	-14	**3.19***	10	6

	-34	-14	-23	**3.12**	5	8
	-16	-7	-15	**3***	5	8
	-19	-23	-13	**2.1***	5	8
	-23	-15	-16	**2.07***		8
	-19	-23	-13	2.61	5	10
	-19	-15	-15	2.4		10
R	21	-39	-3	**3.75**	6	8
	21	-39	-3	**3.27**	17	10
	18	-26	-16	**3.26***		10

Table 4-2: MTL regions specifically engaged in emotional vs. neutral retrieval success activity. The table identifies MTL regions where emotional RS was greater than neutral RS and where neutral RS was greater than emotional RS. The displayed *t* values correspond to the peak voxel for each time point after stimulus onset (where the HDR response was maximal), and represents a significant difference in MR signal between emotion RS and neutral RS. Emotional > Neutral RS = [((Emotional Hits – Misses) – (Neutral Hits - Misses)) ∩ (Emotional Hits - Misses)]. Neutral > Emotional RS = [((Neutral Hits – Misses) – (Emotional Hits - Misses)) ∩ (Neutral Hits - Misses)]. Extent threshold = 5 voxels. ¶regions also surviving FDR-anatomical ROI correction. *regions surviving exclusive masking by incidental encoding. MTL, medial temporal lobe; AMY, amygdala; HC, hippocampus; PHC, parahippocampus; L, left; R, right; RS, retrieval success; Cluster Cor., False Discovery Rate-cluster correction

MTL Regions	Hemisphere	Talairach coordinates			*t* values **Cluster Corrected**	Cluster Size	Time (Sec)
		x	*y*	*z*			
Emotional > Neutral RS							
AMY	L	-19	0	-14	**3.84***	23	6
		-30	-8	-11	**2.88***		6
	R	27	4	-13	**4.16**	5	6
		14	0	-17	**2.56**	6	6
HC	L	-23	-39	4	**3.3***	27	6
		-30	-7	-15	**2.62***		6
		-20	-27	-6	**2.26***		6
	R	18	-11	-18	**3.85***	28	6
PHC	L	-23	-22	-20	**5.75¶***	6	6
		-19	-30	-10	**3.61***	50	6
		-16	0	-12	**6.32***		6

		-27	-22	-23	**2.56***	7	8
	R	21	-11	-22	**3.62***	36	6
		18	-34	-9	**3.54***		6
		14	4	-13	**2.61***		6
Neutral > Emotional RS							
HC	R	25	-39	1	**2.87**	7	8
		21	-31	-2	**3.09**	7	10
PHC	R	18	-26	-19	**2.92***	13	10
		17	-39	-3	**2.38***		10

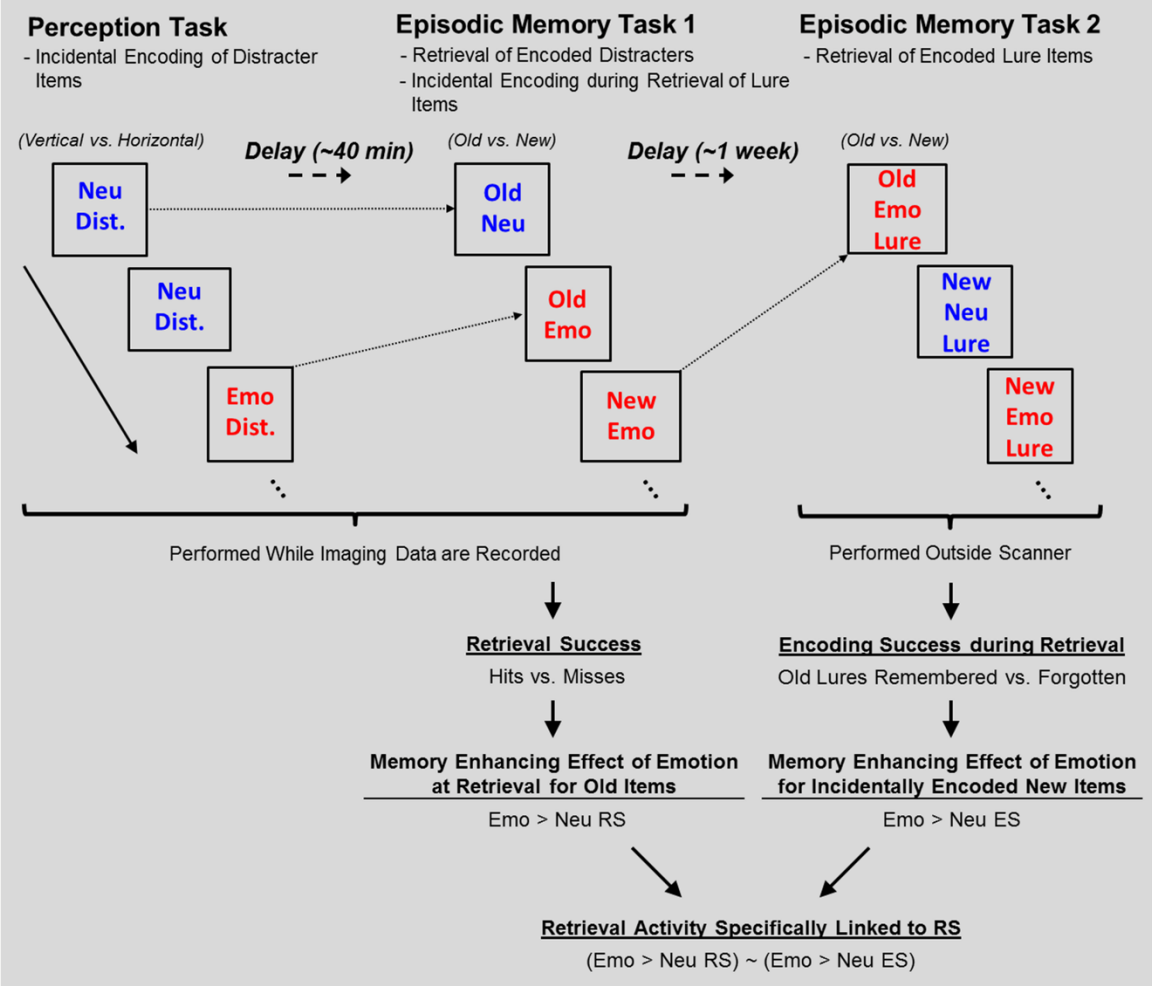

Figure 4-1. Diagram of the Experimental Paradigm. A novel experimental paradigm was implemented to investigate the relationship between retrieval success activity and incidental encoding success activity during retrieval. The perception task required participants to determine the orientation of vertically or horizontally presented pictures with emotional, neutral, or no distraction. Immediately following completion of the perception task, memory for a subset of the pictures presented as distracters during the task was tested in a surprise episodic memory task (EM-1). EM-1 allowed for the examination of the neural correlates of retrieval success to the distracter items incidentally encoded during the perception task, and also served as the "study" phase for emotional and neutral lure items. Approximately one week following the completion of the perception and EM-1 tasks, participants completed another surprise episodic memory task (EM-2), which tested memory for the emotional and neutral lure items used during EM-1. In both memory tasks participants were instructed to determine if the pictures were from the previous task (Old) or never seen before (New*)*. Separation of RS from incidental ES activity was obtained by comparing defining RS as the contrast between Hits and Misses and defining incidental ES as the contrast between Remembered and Forgotten Lure items presented during retrieval. Emo = Emotional; Neu = Neutral; Dist. = Distracter; RS = Retrieval Success; ES = Encoding Success

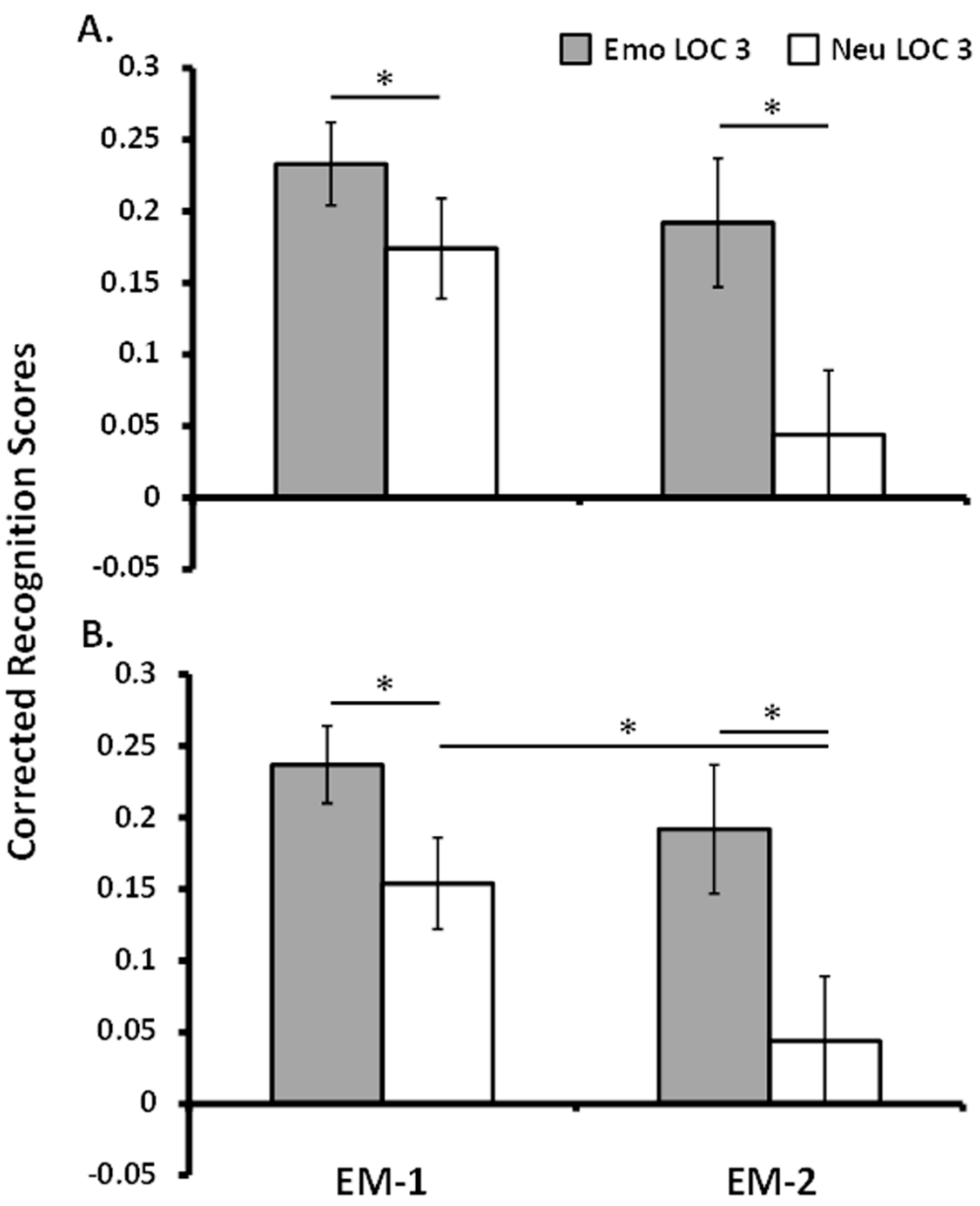

Figure 4-2. Increased Memory for Emotional Pictures. Figure shows corrected recognition scores for Emo and Neu LOC 3 items for EM-1 (left) and EM-2 (right). Memory performance was greater for Emo items than for Neu items in EM-1 and EM-2 (A), which was also identified when tested with the subset of participants that had both EM-1 and EM-2 data (B). There was also a significantly decrease in memory performance for neutral items from EM-1 to EM-2. Emo = Emotional; Neu = Neutral; LOC = Level of Confidence; EM-1 = Episodic Memory task 1; EM-2 = Episodic Memory task 2.

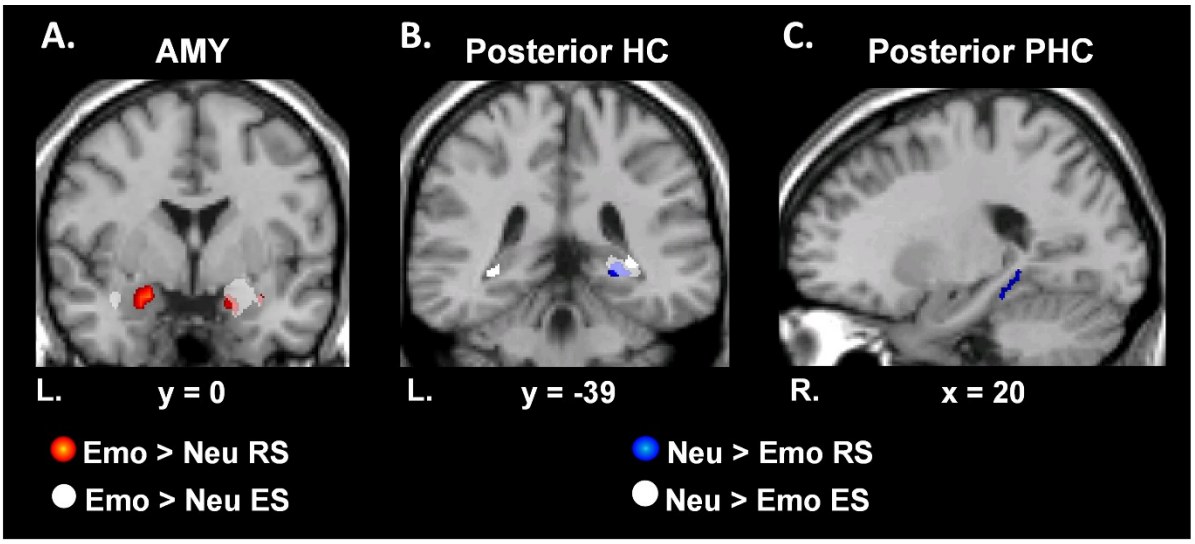

Figure 4-3. Dissociating Retrieval Processes Linked to the Enhancement of Emotional and Neutral Memory. MTL regions sensitive to Emo vs. Neu RS (red) and incidental ES (white) of Emo vs. Neu lure items presented during EM-1. Bilateral AMY activity was identified for Emo > Neu RS, but activity in the right hemisphere was accounted for by incidental Emo > Neu ES activity (A). MTL regions showing greater RS activity for Neu > Emo items (blue) and incidental ES activity for Neu > Emo lure items (white) presented during EM-1. Right HC tail activity was identified for Neu > Emo RS, but was accounted for by encoding-related activity for lures during retrieval (B). RS activity identified in the right posterior PHC, was unaccounted for by encoding related activity (C). Areas indicated in red illustrate the difference in activation in response to Emo > Neu RS, masked with the main effect of Emo RS. The *t* values correspond to the *t* map for Emo > Neu RS. Areas indicated in white on panel A illustrate activation in response to Emo > Neu ES, masked with the main effect of Emo ES. Areas indicated in blue illustrate the difference in activation in response to Neu > Emo RS, masked with the main effect of Neu RS. The *t* values correspond to the *t* map for Neu > Emo RS. Areas indicated in white on panels B and C illustrate the activation in response to Neu > Emo ES, masked with the main effect of Neu ES. These activation maps are superimposed on a high-resolution brain image displayed in coronal (A, B) and sagital (C) views. The Talairach x and y coordinates for the corresponding plane is indicated below each high-resolution brain image. AMY, Amygdala; HC, hippocampus; PHC, Parahippocampus; MTL, Medial Temporal Lobe; RS, Retrieval Success; ES, Encoding Success; Emo, Emotional; Neu, Neutral; L, Left; R, Right; EM-1, Episodic Memory task 1.

CHAPTER 5

THE IMPACT OF EMOTIONAL DISTRACTION ON GOAL-ORIENTED TARGET PROCESSING IN ADOLESCENT PSYCHOPATHOLOGY – ERP EVIDENCE

Electrophysiological Correlates of Fearful and Sad Distraction on Target Processing in Adolescents with Attention Deficit-Hyperactivity Symptoms and Affective Disorders

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Emotion can both enhance and impair cognition and performance (Chan & Singhal, 2012; Dolcos, Iordan, & Dolcos, 2011). For instance, increased attention to emotional stimuli can also lead to distracting effects on cognitive performance if the emotional information is task-irrelevant (Dolcos & McCarthy, 2006; Shafer et al., 2012). These opposing effects of emotion are exacerbated in clinical conditions, such as depression and anxiety, where increased emotional distractibility is observed. This heightened susceptibility to emotional distraction may, in part, be due to faulty regulatory mechanisms that help individuals cope in the presence of unwanted emotional stimuli. The ability to regulate emotion is a complex phenomenon that begins to develop in infancy, and continues through the childhood and adulthood years. Moreover, a healthy set of emotional regulatory strategies are considered to be highly associated with overall positive health states and general wellbeing (Denkova, Dolcos, & Dolcos, 2012; Thompson & Calkins, 2006).

In recent years there have been important advances in the neuroscientific study of emotion and emotion regulation (see Dolcos et al., 2011). In particular, the neural basis of emotion regulation has received considerable research interest because of the compelling argument that certain types of psychopathology are linked to a fundamental *dys*regulation in emotion processing (Davidson, 2002; Phillips, Ladouceur, & Drevets, 2008). This dysregulation has been described as involving an imbalance between basic affective processing and higher-level executive processes including top-down attentional-control (M. K. Johnson et al., 2005). Moreover, in pediatric populations emotion regulation is likely of paramount importance in the development of stable and normal cognitive function over time (Lewis, Lamm, Segalowitz, Stieben, & Zelazo, 2006). It is widely known that psychopathologies with a childhood onset are associated with a higher incidence of relapse, heightened resistance to therapy, and other long-

term varied health problems (Snyder, 2001). It has been suggested that children at risk for depression may be vulnerable to other risks due to trouble with self-regulation of their own emotions as well as receiving inconsistent regulatory management from caregivers and peers due to their reactivity (Thompson & Calkins, 2006). That is, these children may be offered less support and help with alternate strategy formation that is critical for normal development. Similar evidence exists in the attention deficit and hyperactivity disorder (ADHD) literature. Where emotional dysregulation contributes to behavioral excess, impulsive responding, and delayed cognition that ultimately leads to the child's feelings of heightened frustration and interferes with normal development of socio-emotional skills (Walcott & Landau, 2004).

From a neuroimaging point of view, emotion regulation processes have been shown to correlate with activation in dorsal-lateral, medial pre-frontal, and lateral parietal cortices associated with attentional control processes, as well as changes in activation in the amygdala, ventral-lateral and ventral medial prefrontal regions associated with emotional re-appraisal and attenuated emotional reactivity (Beauregard, Levesque, & Bourgouin, 2001; Urry et al., 2006; Yamasaki, LaBar, & McCarthy, 2002). Although much of the relevant cognitive neuroscience literature in this area has been provided by fMRI research, important contributions to this field have also been made through event-related potential (ERP) methods. ERP reflect synchronous post-synaptic neural activity that is time locked to the onset of an eliciting stimulus, and are typically characterized by their peak amplitude, time-to-peak latency, and scalp topography (Luck, 2005). This technique is highly valuable for the study of human cognitive phenomena because they are non-invasive and provide a reflection of neural activity with excellent temporal resolution in the order of milliseconds(Luck, 2005). Thus, they are useful for modelling near simultaneous neuronal activity, while at the same time are highly suitable for studying brain

function in pediatric and clinical populations. The primary focus of the present study was to examine the ERP markers of emotion and emotional regulation in youth suffering from affective and attentional disorders while engaged in an emotional oddball task (modified from Wang, McCarthy, Song, & Labar, 2005) that allowed for the assessment of neural activity in response to both emotional stimuli and non-emotional stimuli requiring attentional control, as well as the interactions between them.

ERP studies of emotion processing employing stimuli from the International Affective Picture System (IAPS), a standardized set of photographs that vary along dimensions such as emotional valence and arousal (Lang, Bradley, & Cuthbert, 2005), identified specific ERP components sensitive to emotion modulation. Using IAPS stimuli, research has shown that emotional images are often associated with an increase in early and sustained attention that presumably facilitates the processing of emotional information, and is reflected by a modulation of the amplitude of the ERPs. For example, both the P100 and the late positive potential (LPP) are well characterized ERP components that are sensitive to modulations by emotion (see Olofsson, Nordin, Sequeira, & Polich, 2008 for a review). The P100 is a positively deflecting waveform that typically occurs between 80 and 200 ms post stimulus onset and has been shown to be a marker of extrastriate activity (Clark, Fan, & Hillyard, 1995). The P100 is the most consistently found early component that can be modified by fearful emotion (Carretie, Hinojosa, Martin-Loeches, Mercado, & Tapia, 2004; Delplanque, Lavoie, Hot, Silvert, & Sequeira, 2004; Eimer & Holmes, 2002; Holmes, Kiss, & Eimer, 2006; Pourtois, Dan, Grandjean, Sander, & Vuilleumier, 2005; Smith, Cacioppo, Larsen, & Chartrand, 2003). While the P100 is commonly modulated by emotion, the topography of the modulation has varied from occipital, to lateral-

occipital, to parietal, to frontal locations. It has been suggested that this fluctuation in topography is largely due to methodological and task effects (Olofsson et al., 2008).

The LPP is a positive deflection that peaks over parietal electrode sites at latencies that are after 300 ms, and is evident throughout the presentation duration of the eliciting emotional picture or word. It has been shown to be larger in amplitude in response to aversive stimuli compared to neutral stimuli, as well as stimuli that are highly arousing (Dolcos & Cabeza, 2002; Schupp, Cuthbert, Bradley, Hillman, & Hamm, 2004; Weinberg & Hajcak, 2010). Moreover, the larger LPP effect in response to emotional stimuli is not sensitive to habituation effects associated with repeated stimulus presentation (Olofsson & Polich, 2007) as is the case of galvanic skin conductance (GSR), electromyography (EMG), and amygdala activation in fMRI (Breiter et al., 1996; Codispoti, Ferrari, & Bradley, 2006, 2007). The LPP appears to require the conscious awareness of the eliciting stimulus (Williams et al., 2007), and shows consistent morphology over time within subjects (Codispoti et al., 2006). In terms of its functionality, it has been argued that the LPP reflects an increase in sustained attention in order to facilitate the extended processing of motivational information, including higher cognitive processes such as memory encoding and retention (Koenig & Mecklinger, 2008). The LPP has been linked to activity in the occipital, parietal, and inferior temporal lobes (Keil et al., 2002; Sabatinelli, Lang, Keil, & Bradley, 2007), perhaps also reflecting downstream activity due to initial emotional modulation of the amygdala (Hajcak, MacNamara, & Olvet, 2010). Despite relatively limited research examining the LPP in children and youth, it has been shown that a measurable LPP is evident in response to emotional face presentation in populations as young as 7 month old (Leppanen, Moulson, Vogel-Farley, & Nelson, 2007). More recently, Hajcek and Dennis (2009) showed that the LPP is larger in response to emotional compared to neutral content in IAPS

stimuli in children, and it has been suggested that children who have suffered abuse elicit larger LPP waves to stimuli that portray threatening and anger situations (Shackman, Shackman, & Pollak, 2007). Moreover, it has been argued that since the LPP is a viable marker of fear-based processing, it may be useful as an indicator of emotional dysregulation in clinical populations, including pediatric affect disorders (Solomon, DeCicco, & Dennis, 2012).

Another ERP component that has been shown to be strongly related to attention and also emotion processing is the P300, which is observed as a large positive waveform maximal over midline central and parietal electrode sites peaking between 300 and 500 ms after stimulus onset (Sutton, Braren, Zubin, & John, 1965). Extensive literature supports the idea that the P300 wave has multimodal generators (Kok, 2001) and peaks once a task relevant stimulus has been evaluated. It is typically observed when attention is paid to a stimulus train which has both frequent and infrequent (oddball) trials. It has been shown that the peak latency of the P300 increases if the categorization of a target stimulus becomes more difficult suggesting it is also involved in low level perception (Coles, Smid, Scheffers, & Otten, 1995; Kutas, McCarthy, & Donchin, 1977). There is an agreement that P300 amplitude reflects the intensity of processing (Donchin, Karis, Bashore, Coles, & Gratton, 1986; Donchin, Kramer, & Wickens, 1986) as well as perceptual-central resources (Donchin, Karis, et al., 1986; Kramer & Spinks, 1991) within a multiple capacity framework (Singhal & Fowler, 2004, 2005; Wickens, 1984). In a study co-registering ERP and fMRI data, the brain networks underlying the visual P300 (oddball P3b) were localized to both parietal cortex and inferior temporal cortex (Bledowski et al., 2004). It has also been long argued that the multimodal nature of P300 is likely due to significant frontal lobe contribution (R. Johnson, Jr., 1993). The P300 has been shown in some studies to be larger in response to affective images compared to neutral images (Carretie et al., 2004) and this effect

has been attributed to the idea that emotion directs the allocation of attention and, it has been further argued that emotional stimuli are "natural targets" because of their strong salience and motivational relevance (Johnston, Miller, & Burleson, 1986; Sabatinelli, Bradley, Fitzsimmons, & Lang, 2005). In the context of emotion regulation, it has been argued that the amplitude of P300 may reflect the amount of cognitive resources allocated to the processing of information that follows an emotional stimulus (Ellis & Ashbrook, 1988). Further, it has been suggested that this process may function to critically subserve regulatory processes (Deveney & Pizzagalli, 2008).

Previous research examining emotion regulation and attentional control in youth suggests that this population may be less well equipped to properly inhibit unwanted allocation of their attentional resources toward distracting emotional information. Furthermore, youth suffering from mental health concerns including attentional and affective disorders may have more difficulty with this type of inhibition. However, to date the underlying neural mechanisms of this phenomenon have not been fully elucidated. The primary research purpose of this study was to examine the nature of these emotion and attention ERP markers (i.e., P100, LPP, P300) in a population of youth with potential dysfunction in emotion regulation and attention because they had been diagnosed with symptoms related to affective disorders and ADHD. To that end, adolescents suffering with mental health problems and a healthy control group of participants performed a modified version of the emotional oddball paradigm (after Wang et al., 2005), that allowed for the assessment of emotion processing, goal directed attentional processing, and the interaction between the two. For distracter processing, we predicted differences in behavioural and ERP data such that reaction time (RT) would be delayed and early and late ERP components would be modified by emotional images compared to neutral distracter images. Specifically, the

P100 and LPP amplitude would be enhanced by affective compared to non-affective distracters .For target processing, we predicted differences in behavioural and ERP data such that RT and P300 amplitude in response to targets would differ as a result of the preceding distracter type. Moreover, we predicted that the pattern of behavioral and neural responses for both distracters and targets would be different between our clinical and healthy control groups.

Methods

Participants

Twenty-seven (ten male, two left-handed) adolescents (12 – 17 years; average age = 14.3; SD = 1.27) were recruited from a residential mental-health treatment facility in the City of Edmonton, Alberta, Canada. These individuals were clinically diagnosed with DSM-IV Axis-1 disorders including ADHD combined, predominantly inattentive type, and predominantly hyperactive/impulsivity type, oppositional defiant disorder, conduct disorder, depressive disorders (major depression and dysthymia), and anxiety disorders (including generalized anxiety disorder; posttraumatic stress disorder; and anxiety disorder). Clinical characteristics of these participants were summarized in Table 1. For summary purpose, we grouped depressive disorders and anxiety disorders as distress disorders. As shown in Table 1, there were pre-existing or co-occurring co-morbidities. Six healthy control adolescents were recruited from the City of Edmonton (three male, 13 – 16 years, average age = 14.67; SD =1.21).All participants had normal or corrected-to-normal vision. Informed consent and assent were obtained from parental guardians and participants before participating. The experimental protocol was approved for ethical treatment of human participants by the Health Research Ethics Board at the University of Alberta. Event-related potential data was assessed on a subset of ten (five male, one left-

handed) clinically diagnosed adolescents (13 - 16 years; average age = 14.1 years; SD = 1.2) and all six healthy control (non-clinical) adolescents.

[Insert Table 1 about here]

Task and Stimuli

Participants performed a modified version of the emotional oddball paradigm (Wang et al., 2005) which consisted of frequent stimuli serving as the baseline [scrambled pictures, 79% (465 trials)], infrequent distracters and oddball targets, 21% (124 trials). Infrequent distracters consisted of sad and fearful pictures (13 trials each), neutral pictures (26 trials); and positive pictures (4 trials). The oddball targets (circles) were sub-grouped according to their preceding infrequent stimulus type [i.e., target-after-sad (11 trials), target-after-fear (11 trials), target-after-target (24 trials), and target-after-neutral stimuli (22 trials)]. To ensure that sad and fear pictures were paired to a neutral picture that possessed similar visual qualities (e.g., sad picture = man sitting and crying; neutral picture = another man sitting with no overt emotional expression), the neutral pictures were originally subdivided into neutral paired with sad and neutral paired with fear However, for analyses these separate neutral categories were collapsed resulting in one neutral picture and one target-after-neutral category. Positive pictures only served as emotional anchors, to provide a context for ratings, and were not included in the analyses. The infrequent distracter stimuli (sad, fearful, and neutral pictures) were selected from IAPS based on normative ratings for valence and arousal and were supplemented with in-house pictures used in previous studies (Wang, Huettel, & De Bellis, 2008; Wang et al., 2005). Participant's ratings of the distracter categories did not differ between the clinical and non-clinical groups, $F(4, 80) = 0.3$, $p = 0.88$ for valence and, $F(4, 80) = 0.34$, $p = 0.85$ for arousal. There was main effect of valence, $F(2, 80) = 129.55$, $E = 0.65$, $p < 0.001$, and a main effect of arousal $F(2, 80) = 44.22$, $E = 0.79$, p

< 0.001. The fear images were rated as most negative (fear>sad>neutral) and most arousing (fear>sad>neural). The mean valence/arousal scores for each distracter type rated by the 27 clinical adolescents (on a scale from 1 to 9) were as follows: 5.22/2.48 for neutral; 2.65/5.22 for fear; and 2.87/4.04 for sad. The mean valence/arousal scores rated by the 10 ERP clinical adolescents were as follows: 5.34/2.32 for neutral; 2.58/4.62 for fear; and 2.83/3.42 for sad. The mean valence/arousal scores as rated by the 6 non-clinical adolescents were as follows: 5.3/2.21 for neutral; 2.4/5.33 for fear; and 3.05/3.97 for sad. The infrequent circle targets varied in size and color so that each target stimuli was unique. The frequent distracter stimuli (scrambled pictures) were digitally scrambled versions of the picture stimuli and thus contained the same average spatial frequency and luminance as the emotional and non-emotional pictures. Participants made one button press to all frequent (i.e., scrambled pictures) and infrequent (i.e., neutral, sad, and fear pictures) stimuli, and they made another button press to all target stimuli.

Event-Related Potential (ERP) Recording and Analyses

ERPs were recorded using a high-density 256-channel Geodesic Sensor Net (Electrical Geodesics Inc, Eugene, OR), amplified at a gain of 1000 and recorded at a sampling rate of 250Hz (impedance < 50 KΩ and initially referenced to the vertex electrode (Cz)). Using Netstation (Version 4.4.2, Electrical Geodesics Inc, Eugene, OR), data were bandpass filtered from 0.1-30 Hz, grand average re-referenced offline, and segments were constructed around events of interests from 300 msec pre-stimulus to 800 msec post-stimulus. Data were also baseline corrected (-300 to 0 ms), and corrected for eye-movement artifacts. A minimum of 5 epochs per condition were necessary for the participant to be included in ERP analyses. The individual waveforms were visually inspected, and clear components of interests (i.e., P100, P300, LPP) were identified for each participant at or near electrodes sites shown in prior

literature to display maximal amplitudes. More specifically, because our primary goal of the study is to investigate emotional dysregulation effects on cognition in a clinical population, we first investigated significant effects in the clinical group. A secondary analysis on the non-clinical group data was performed for confirmation .Thus, analyses were observation-driven with ERP inspection in the clinical group for distracter and target ERPs at cardinal electrode clusters. Significant effects that were identified in the clinical group were then compared to the corresponding electrode sites in the non-clinical control group. Mean amplitude data for late (LPP, P300) ERP components and maximum amplitude data for early (P100) ERP components were then extracted. Time windows for each component were determined from visual inspection and were 300 - 549 msec post stimulus for the P300, 550 - 800 msec post stimulus for LPP, and 100 - 200 msec post stimulus for P100. Since data was acquired with a high-density net consisting of 256 electrodes, we also employed an extent threshold of 3 adjacent electrodes for all components of interests.

Experimental Procedures

The oddball trials (i.e., infrequent distracters and target stimuli) were divided into four runs of 25 trials and one run of 24 trials. To avoid induction of mood states, the negative distracter oddball trials within each run were pseudorandomized so that no more than two trials of the same valence type were consecutively presented. The inter-trial interval was 2 seconds. Each trial started with the presentation of a stimulus (frequent, infrequent distracter or a target) presented for 750 msec and was followed by a fixation screen for 1250 msec. To prevent the participants from anticipating the occurrence of a stimulus the interval between rare stimuli (i.e., the infrequent distracters and targets) was randomized on an exponential distribution with a median of 8 sec and a range between 6 and 10 seconds (See Figure 1). The participants' task was

to indicate whether the stimulus was a target or non-target by pressing a button. Participants were instructed to make a right hand button press any time they saw a target (circle) and a left hand button press to all other stimuli (i.e., frequent scrambled and infrequent sad, fearful, neutral, and positive distracters). Participants were also instructed to respond as soon as the image was presented and to respond as quickly and as accurately as possible, and to experience any feelings and thoughts the pictures might trigger.

[Insert Figure 1 about here]

Statistical Analyses

For comparison of clinical and non-clinical groups, behavioral (reaction time, RT) and ERP (P100 max amplitude; P300 and LPP mean amplitude) data in response to distracters and targets were analyzed via two separate mixed model Analyses of Variances (ANOVA) tests. For each ANOVA the between subject variable was Group (Clinical, Non-clinical). For the distracter ANOVAs the within subjects variable was Distracter Type (Neutral, Fear, Sad), while for the target ANOVAs the within subject variable was Target Type (Target-after-Target, Target-after-Neutral, Target-after-Fear, Target-after-Sad). These mixed model analyses were performed using the clinical group (n = 10) that had both behavioral and ERP data. For within group comparisons one-way repeated measures Analyses of Variances (ANOVA) were performed for distracter and target data. The distracter ANOVA assessed responses to the infrequent sad, fearful, and neutral distracters. The target ANOVA assessed responses to the targets as a function of the preceding rare stimulus type (i.e., target-after-target; target-after-neutral; target-after-sad; target-after-fear). For all analyses the p-value corresponding to the Greehouse-Geisser correction is reported. The epsilon values are reported only where significance was found. Post-hoc comparisons were performed where appropriate using the Fisher LSD test. The within group analyses were

performed on all three groups (i.e., non-clinical, clinical with 10 participants, clinical with 27 participants) separately. In the behavioral analyses trials were excluded if they were incorrect and if reaction time (RT) data were ≤ 175 msec or ≥ 2000 msec. While error rates were significantly greater for target (M = 12.4 %, SE = 2.4%) compared to distracter (M = 4.1 %, SE = 1.4%) stimuli, $F(1, 40) = 8.84$, $p = 0.005$,they did not differ as a function of group, $F(2, 40) = 0.91$, $p = 0.41$, nor did they differ within stimulus type (i.e., within distracter and target stimuli), $F(2, 80) = 0.93$, $p = 0.4$, for distracters and $F(3, 120) = 0.16$, $p = 0.93$, for targets. For the ERP analyses, all trials were included in the analyses as the number of trials usable after data processing was low.

Results

Increased Behavioral Impact of Fearful Distracters

Processing of fearful distracters was associated with longer reaction times in both clinical and control groups. There were no differences between clinical (n=10) and non-clinical adolescents (n = 6) in RT to distracters, $F(1,14) = 0.004$, $p = 0.95$, or the Distracter Type x Group interaction, $F(2, 28) = 0.05$, $p = 0.86$. There was a main effect of Distracter Type, $F(2, 28) = 8.35$, $E = 0.59$, $p = 0.008$, and post-hoc comparisons using Fisher LSD test showed RT to fear distracters was significantly longer than to neutral, $p = 0.006$, and sad, $p = 0.01$ distracters, where the later two type of distracters were not different from each another, $p = 0.48$. Assessing the effect of Distracter Type on RT for each group separately showed that the same pattern was present for both clinical, $F(2, 18) = 4.11$, $E = 0.58$, $p = 0.065$, and non-clinical, $F(2,10) = 9.18$, $E = 0.66$, $p = 0.017$, adolescents. Similar to the above results for the clinical sub-sample of 10 and the non-clinical sample of 6, the analysis on RT data for all 27 participants also showed a main effect of Distracter Type, $F (2, 52) = 7.57$, $E = 0.071$, $p = 0.004$. Post-hoc comparisons using

Fisher LSD test showed longer RT to the fearful distracters than to neutral ($p = 0.002$) or sad ($p = 0.009$) distracters, but the latter two were not significantly different from each another ($p = 0.45$). (See Table 2 for mean and standard error RT data for each distracter category for clinical samples of 27 and 10 and the non-clinical sample of 6).

[Insert Table 2 about here]

ERP Evidence of Increased Processing of Fearful Distracters in Clinical Adolescents

The ERP data revealed an impact of Distracter Type and Group for both early (P100) and late (LPP) components in response to the distracter images. First, the P100 amplitude at right hemisphere occipital-temporal electrodes (P10 in 10-10 topography) showed a significant interaction between Distracter Type and Group, $F(2, 28) = 4.41$, $E = 0.88$, $p = 0.027$, but no main effect of Distracter Type [$F(2, 28) = 0.92$, $p = 0.4$] or Group [$F(1, 14) = 2$, $p = 0.2$] effect. There was a main effect of Distracter Type for the clinical sample, $F(2, 18) = 3.83$, $E = 0.91$, $p = 0.047$, where replicating the observed behavioral pattern, post-hoc comparisons using Fisher LSD test showed overall the amplitude was larger for fearful images relative to both neutral ($p = 0.02$) and sad ($p = 0.05$), where the later two were not different from each another ($p = 0.82$), see Figure 2, left panel. Whereas, for the non-clinical sample there was no effect of Distracter Type on P100 amplitude, $F(2, 10) = 1.99$, $p = 0.2$, see Figure 2, right panel, and Table 3.

[Insert Figure 2 about here]

There was no Distracter Type x Group interaction effect for the LPP at the left, midline, or right parietal electrodes (P3, Pz, P4 in 10-10 topography), $F(2, 28) = 1.78$, $p = 0.19$, nor was there a main effect of Group, $F(1,14) = 1.17$, $p = 0.3$. However, there was a significant effect of Distracter Type, $F(2, 28) = 5.1$, $E = 0.81$, $p = 0.02$. Analyses examining the effect of Distracter Type on parietal LPP amplitude for clinical and non-clinical samples separately found a main

effect of Distracter Type for clinical, F(2,18) = 9.52, E = 0.94, p = 0.002, but not non-clinical adolescents, F(2,10) = 0.48, p = 0.55, see Figure 3. Post-hoc comparisons for the clinical data using Fisher LSD test identified a pattern similar to the behavioural and P100 data with this main effect driven by larger mean amplitude in response to fearful distracters compared to neutral (p = 0.001) and sad (p = 0.01) distracters, again there were no difference between sad and neutral distracters (p = 0.69), see Figure 3, left panel, and Table 3. There was no effect of Distracter Type, F(2, 28) = 0.12, p = 0.84, Group, F(1, 14) = 0, p = 1, or Distracter Type x Group interaction, F(2, 28) = 0.5, p = 0.57, on P300 amplitude measured at parietal electrodes.

[Insert Figure 3 about here]

Left temporal electrodes (TP7 in 10-10 topography) showed a main effect of Distracter Type, F(2, 28) = 10.57, E = 0.87, p = 0.001, but no main effect of Group, F(2, 14) = 2.75, p = 0.12, or Distracter Type x Group interaction, F (2, 28) = 0.19, p = 0.8. Pairwise comparison using Fisher LSD test showed LPP mean amplitude was larger for fear compared to neutral distracters (p = 0.009) and the neutral distracters mean amplitude was larger compared to sad distracters (p = 0.08) (i.e., fear>neutral>sad). Investigation of the LPP for clinical and non-clinical samples separately revealed a main effect of Distracter Type for the clinical sample, F(2, 18) = 9.21, E = 0.96, p = 0.002, and a trend effect for the non-clinical sample, F(2, 10) = 3.08, E = 0.58, p = 0.09, see Figure 4. Post-hoc comparisons using Fisher LSD test showed for the clinical group the amplitude to fear distracters was larger than to neutral distracters (p = 0.02), which were no different from the amplitude to the sad distracters (p = 0.14) (i.e., fear>neutral=sad). Post-hoc comparisons for the non-clinical samples showed no significant differences between distracter types, even though the pattern was in the same direction as for the non-clinical sample (see Table 3).

[Insert Figure 4 and Table 3]

ERP Evidence for Modulation of Target Processing by Emotional Distraction in Clinical Adolescents

For RT data, there were no significant effects of Target Type, $F(3, 42) = 0.7$, $p = 0.51$,or Group, $F(1, 14) = 1.56$, $p = 0.23$, or an interaction between Target Type and Group, $F(3, 42) = 0.25$, $p = 0.8$. Neither the clinical or non-clinical samples showed a main effect of Target Type on RT, $F(3, 27) = 0.44$, $p = 0.66$ and $F(3, 15) = 0.54$, $p = 0.54$, respectively. Analysis on the larger clinical sample using all 27 participants also did not show a main effect of Target Type on RT data, $F(3, 78) = 1.38$, $p = 0.26$, although the larger analysis showed a trend level effect of sad distracter images on performance, where targets-after-sad had slower response times compared to targets-after-targets, $t(26) = 1.89$, $p = 0.07$. See Table 2 for mean and standard error RT data for each target category.

Event-related potential data for the P300 at left parietal electrodes (P5, P3 in 10-10 topography) showed no main effect of Target Type, $F(3, 42) = 1.8$, $p = 0.18$, or Group, $F(1, 14) = 0.11$, $p = 0.74$ nor a significant interaction between Target Type and Group, $F(2, 42) = 1.8$, $p = 0.18$. While this overall model was not significant, examination of Target Type for clinical and non-clinical samples separately, showed a marginal effect of Target Type for the clinical sample, $F(3, 27) = 2.86$, $E = 0.67$, $p = 0.08$, but not for the non-clinical sample, $F(3, 15) = 1.68$, $p = 0.24$. For the clinical group, post-hoc comparisons using Fisher LSD test showed that P300 amplitude to target-after-sad was larger than target-after-target ($p = 0.03$), while the amplitude to target-after-fear was marginally larger than to target-after-target ($p = 0.07$), see Figure 5 and Table 3.

[Insert Figure 5 about here]

In addition to the P300 results reported above, a main effect of Group, $F(1, 14) = 4.48$, $p = 0.05$, with the clinical group having overall smaller amplitudes compared to the non-clinical group, and a marginal Target Type x Group interaction, $F(3, 42) = 2.78$, $E = 0.74$, $p = 0.07$, was identified for LPP mean amplitude over left hemisphere temporal-occipital electrodes (TP7, P7, P07 in 10-10 topography), see Figure 6 and Table 3. There was no main effect of Target Type, $F(3, 42) = 1.92$, $p = 0.16$. To determine the effects driving the interaction, separate ANOVAs were performed on the clinical and non-clinical groups. There was a main effect of Target Type for the clinical group, $F(3, 27) = 3.69$, $E = 0.7$, $p = 0.04$, but not the non-clinical group, $F(3, 15) = 2.09$, $p = 0.18$. Further investigation of the main effect of Target Type in the clinical group using Fisher LSD tests showed target-after-fear and target-after-sad mean amplitudes to be larger than target-after-target, $p = 0.05$ and $p = 0.02$, respectively.

[Insert Figure 6 about here]

Discussion

The main purpose of this study was to examine the morphology of ERP markers of emotion and attention in response to stimuli presented in an emotional oddball task with a group of youth primarily suffering from disorders of attention and emotion regulation. Analyses were performed on three sets of data: two from clinical samples (with or without ERP data), and one from the control sample. The task employed allowed for the comparison of behavioral and ERP responses to distracter pictures that were fearful, sad, or neutral, as well as target stimuli that were circles, which contained no emotional content. We performed analyses on the distracter events themselves (all picture types) as well as the target events that immediately followed distracters (fearful, sad, neutral) or other targets. Our study yielded three main findings. First, we identified an increased impact of fearful distracters on behavioral performance and this

difference was found for both clinical and non-clinical samples. Second, in clinical adolescents, this behavioral difference corresponded to an increase in the amplitude of early and late emotion ERP components in response to fearful relative to neutral distracters. Lastly, clinical adolescents exhibited difference in ERP morphology to targets following emotional distraction.

Increased Behavioral Impact of Fearful Distracters

The behavioral finding in our study was that we observed longer RT in response to the fearful distracters compared to sad or neutral distracter images. We observed this fearful effect in all three of our samples, the large group of 27 participants the smaller group of 10 participants and the control group of 6 participants. This suggests that from a behavioural perspective, all three of our adolescent groups were similar and that our smaller subset clinical group is representative of the larger clinical cohort in our study. These findings show that all our participants were spending a longer time in the preparation and execution of a manual response to the fearful pictures. This delay can be interpreted as reflecting an increase in the capture of attention by the fearful images compared to sad or neutral (Ohman, Flykt, & Esteves, 2001), even though they were not the main target stimuli in the task (Vuilleumier & Schwartz, 2001). Thus, the fearful images may have competed more for attention related resources, which led to impaired performance (Denkova et al., 2010; Dolcos & McCarthy, 2006; Zanto & Gazzaley, 2009). The error rates were equivalent across all conditions, and so the differences in RT that we observed are not due to simple speed-accuracy trade-off effects. We also observed a trend in the target RT data for the large group of 27 clinical participants, where responses to targets that followed sad images were slightly slower than responses to targets that followed other targets. We are cautious to interpret this effect because our control sample is very small in comparison to the larger clinical sample, but in light of the P300 differences (discussed below), these findings

are consistent with a carry-over-effect of the emotion from the affective pictures on the perception and decision making processes required for target response.

ERP Evidence of Increased Processing of Fearful Distracters in Clinical Adolescents

In response to the distracter pictures, we observed early and late effects in the P100 and LPP waveforms, respectively. In the case of the P100 we unexpectedly observed larger amplitudes in response to the fearful images compared to the other image types at right hemisphere occipital-temporal electrodes. Importantly, this effect was only observed in the clinical sample, and was not present in the healthy control sample. It is well known that the P100 reflects early spatial attention operations associated with activity in extra-striate brain regions (Martinez et al., 1999), and it is one of the earliest endogenous ERP components that is sensitive to top-down control mechanisms. Thus, on the face of it this pattern of data suggests that the clinical group participants were likely allocating more attention-based resources toward images that were fearful in nature compared to the other image types. Moreover, the healthy control sample did not show evidence of this attentional strategy.

In the case of the LPP at parietal and temporal electrodes we observed larger amplitudes in response to the fearful images compared to the other two image types in the clinical sample. This effect is consistent with the RT data in response to the fearful images. Again, as with the P100 results, this pattern of data was absent in the control sample data, as there were no differences in LPP amplitude across the image types in the healthy control group; also, this effect is inconsistent with the behavioral data. The LPP has been shown to be sensitive to the arousal level of eliciting pictures (Schupp et al., 2004) and this effect appears to be verified in our data. Our ratings clearly show that the fearful images were also the most arousing. Moreover, our fear-based LPP result in the clinical sample may reflect the conscious awareness and salience of the

images (Williams et al., 2007) that results from downstream processing of emotional information perhaps associated with amygdala activity (Bradley et al., 2003). Taken together with research showing that LPP amplitude correlates with anxiety level in healthy adults (MacNamara, Ferri, & Hajcak, 2011) and in youth with anxious attachment styles(Zilber, Goldstein, & Mikulincer, 2007), we may have observed a unique signature of anxiety and arousal associated with fear processing in our clinical population of adolescents. That is, the salience of the fear images is perceptually and cognitively heightened in our special population possibly due to a pre-existing susceptibility for fear-based reactivity.

Critically, this pattern of data was not present in the healthy control sample, which further supports our argument that our clinical adolescent group has a unique processing style for emotional information. This is particularly evident for the fear-based stimuli. Also, in the case of the healthy sample, the ERP data did not follow the behavioral data as it did in the clinical data. This finding may be explained by the small sample size of our healthy control group that makes it difficult to identify reliable physiological differences in distracter processing between groups. It could also be due to individual differences in processing of fear-based stimuli in non-clinical individuals. One other possibility is that the unique mechanisms in fear processing we observed are not intimately linked with behavior in our task. Rather, the ERP effects may reflect processes unrelated to the conscious awareness of the stimulus that are reflected in the response selection and execution process .When the LPP data is considered in conjunction with our P100 data in response to the distracter images in the clinical sample, our ERP data may be a reflection of very early attention modulation in our clinical youth population that is associated with a heightened focus toward the fearful images. The P100 is known to have neural generator sources in similar occipital-temporal regions that also underlie the LPP generation (Bradley et al., 2003), and the

similar fear-based effects we observed in these two waveforms may have been facilitated by a common neural substrate related to projections between sensory and affective brain regions in our special clinical sample.

ERP Evidence for Modulation of Target Processing by Emotional Distraction in Clinical Adolescents

The ERP in response to the target stimuli that we analyzed were the P300 and the LPP. The P300 is a well-known marker of selective attention, perceptual processes and working memory processes (Kok, 2001). In our clinical sample at left parietal sites, the P300 was larger to targets that followed sad images and slightly larger to targets that followed fearful images compared to when targets followed other targets. These differences were absent in the control sample data. Thus we observed a target processing effect related to the preceding emotional stimuli that presumably was related to some carryover effect. This does not follow the behavioral data that showed no differences in RTs to targets following emotional images compared to targets that followed other targets. However, the P300 measure appears to be more sensitive to these putative carry-over effects than behavior, perhaps because P300 reflects perceptual processes rather than response related processes (Kok, 2001), whereas the RT measures must reflect all operations that are engaged between stimulus presentation and response execution. Finally, the LPP data in response to targets showed a strong effect over left temporal sites where amplitudes were larger for targets following both fearful and sad images compared to targets that followed other targets. Again, this finding was only for the clinical sample, and this finding follows the P300 result over left parietal sites and may be a unique reflection of the sustained emotion processing that occurred and affected the target related processes reflected by the P300. Thus, whereas P300 may reflect the increase in attention related resources toward a stimulus

following an emotional image in our clinical population, the LPP effect in response to targets may be more of a reflection of the sustained duration of the neural representation of the emotion itself (Hajcak et al., 2010). That is, a sustained downstream reflection of lower level processes in the amygdala and other affective structures. This sustained activity may result from the inability to disengage from processing emotional information triggered by the distracters (e.g., recollection of negative memories cued by the negative pictures), which continues after the cues disappear and affect the ability to focus on the following targets. This is consistent with mood congruent effects of emotion on memory and may be linked to emotion dysregulation as in the case of post-traumatic stress disorder (McFarlane, 2010). Importantly, this pattern of effects was absent in the control sample.

Caveats. *A*lthough the findings presented shed light on emotion-attention interactions in clinical compared to non-clinical adolescents, the present investigation also has limitations. First, the sample size in both the clinical and non-clinical ERP groups was relatively small. It should be under consideration that with a large sample these effects may slightly change. For example, a common finding in the emotion ERP literature is an enhanced LPP to high arousing emotional relative to neutral stimuli and even though we did not replicate this finding in our healthy control group, we clearly see a trend towards a significant LPP to fear stimuli (see Figures 3 and 4). However, in light of this, our findings are consistent with an exacerbated LPP response to high-arousing emotional stimuli in clinical compared to non-clinical populations (Hajcak & Dennis, 2009). Furthermore, despite differences in the size of the behavioral only (N=27), behavioral and ERP (N=10), and control (N=6) samples, the pattern of behavior was equivalent between all groups. We also acknowledge that our criterion of a minimum of 5 ERP trials per condition is low. A second limitation is co-morbid nature of the diagnoses in our clinical group. In fact, only

one adolescent had been diagnosed with a single mental health disorder, and all others presented with two, sometimes three different disorders. Most undoubtedly the underlying neural mechanisms of these varied diagnoses differ from one another, however, and as shown here there may be some overarching abnormalities in processing that can be identified using electrophysiological measures. A third limitation of the study is the varied medication of the clinical adolescents and within our sample it is impossible to rule out the effects of medication on behavioral and ERP performance. It is possible that the behavioral measures in task performance were insensitive to group differences and those group differences observed with ERP measures were mitigated by the effects of these medications. Future studies using a similar experimental design and a larger number of subjects should further investigate these issues.

Conclusion

Our small scale but complex study is unique in that it has examined both behavioral and ERP responses to stimuli in an emotional oddball task with a sensitive population of adolescents suffering from Axis-1 disorders including ADHD, anxiety, and depression. Moreover, we included a small sample of healthy controls individuals for comparison purposes. Overall we observed an interesting pattern of behavioral (RT) and neural responses (P100, LPP, P300) that showed similarities (i.e., behavioral data) and differences (i.e., ERP data) in emotion and attentional processing between clinical and non-clinical samples. Fearful images impacted behavioral performance for both clinical and non-clinical samples, showing a consistent behavioral effect of fearful emotion regardless of potential underlying alterations in the neural mechanisms of emotion processing between groups. Early (P100) and late (LPP) ERP components assessing emotion processing differentiated between groups as clinical adolescents showed augmented amplitudes to fearful relative to sad and neutral pictures. Furthermore,

emotion modulation of attentional processing (P300) and a sustained emotion effect on target processing (LPP) were identified for the clinical sample only. Suggesting attentional-control processes in our sample of clinical adolescents were more susceptible to emotion modulation through either an increase in the initial engagement of resources or the inability to disengage from the emotional information. Taken together, these data may reflect a pattern of emotion dysregulation in adolescents suffering from Axis-1 disorders that modulates certain aspects of emotion-attention interactions. These effects did not uniquely follow the behavioral responses and perhaps reflect emotion and cognition processes that are not part of the response selection and execution process. Moreover, our results provide an example of the impairing effects that emotion and emotional reactivity can have on very basic cognitive function in sensitive individuals, but not in more robustly healthy persons. Thus, we have provided a small window into potential dysfunction between emotion and cognition in this youth population with clinical disorders.

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Table 5-1: Diagnostic and medication information for the 27 clinical adolescents.

Diagnosis	Number (Male /Female)	Medication (number of patients)			
		None / Unknown	Stimulants	Anti-depressants	Others
ADHD co-morbid with one or more following disorders					
ODD,OCD, PCRP,SRC, RAD,IED , Conduct Disorder, Learning Disorders	10 5 / 5	3 / 1	5	SSRI – 2 NRI – 1	Atypical antipsychotic – 2 Benzodiazepine– 1 β- adrenergic receptor agonist – 1
Distress disorders (one or more of the following: *major depression, dysthymia, anxiety GAD, PTSD, Social phobia)*	4 2 / 2	1 / 0	2	SSRI – 2	Atypical antipsychotic – 1
Distress disorder					
Major Depression	1 0 / 1	–	–	SSRI – 1	Atypical antipsychotic – 1
Distress disorders (major depression, dysthymia, GAD, PTSD)co-morbid with one or more following disorders					
Distress Disorder	1 1 / 0	–	–	NDRI – 1	Atypical antipsychotic – 1
ODD,PCRP,SRC, RAD, conduct disorder, substance abuse, sexual abuse	8 1 / 7	–	2	SSRI – 7 NDRI – 2 NRI - 1	Atypical antipsychotic – 4 Benzodiazepine – 1
Others:two or more following disorders					
ODD, PCRP, conduct disorder	3 1 / 2	3 / 0	–	–	–
Total	27 (10/17)	7 / 1	9	SSRI – 12 NDRI – 3 NRI – 2	Atypical antipsychotic – 9 Benzodiazepine – 2 β- adrenergic receptor agonist – 1

ADHD=attention-deficit/Hyperactivity disorder; ODD= Oppositional Defiant Disorder; OCD=obsessive-compulsive disorder, PCRP=Parent-Child Relation problem; RAD=Reactive Attachment Disorder of Infancy or Early Childhood; SRC=Sibling-Relational Conflict; IED=Intermittent Explosive Disorder; SSRI= selective serotonin reuptake inhibitors; NRI=norepinephrine reuptake inhibitors; NDRI = norepinephrine-dopamine reuptake inhibitors.

Table 5-2: Mean reaction time (RT) and standard error (SE) data to distracters and targets for both the large sample of 27 participants and the small sample of 10 participants.

Distracter Type	**Group**	Neutral	Fear	Sad	
RT (SE)	Clinical n = 27	578.49 (24.63)	629.43 (32.48)	568.59 (23.18)	
	Clinical n = 10	620.65 (47.08)	699.54 (64.24)	619.77 (47.92)	
	Non-clinical n = 6	633.38 (70.17)	704.65 (57.07)	617.95 (65.38)	
Target Type	**Group**	Target-after-Neutral	Target-after-Fear	Target-after-Sad	Target-after-Target
RT (SE)	Clinical n = 27	527.91 (16.02)	536.98 (17.89)	538.31 (18.27)	526.45 (15.85)
	Clinical n = 10	555.94 (26.18)	557.61 (25.19)	548.62 (31.04)	544.5 (24.15)
	Non-clinical n = 6	502.81 (31.07)	499.11 (26.01)	515.9 (20.87)	498.88 (24.76)

Table 5-3: Mean ERP amplitudes and standard error (SE) for the LPP, P100 and P300.

ERP Component	Electrode Cluster	Group	Distracter Type		
			Neutral	Fear	Sad
P100	R. Occipital-Temporal	Clinical n = 10	8.76 (0.79)	11.37 (1.33)	8.48 (1.25)
		Non-clinical n = 6	9.03 (1.29)	6.22 (1.5)	7.02 (1.42)
LPP	Parietal	Clinical n = 10	3.36 (0.98)	6.34 (1.18)	3.92 (0.95)
		Non-clinical n = 6	6.34 (1.26)	6.8 (1.52)	5.76 (1.22)
	L. Temporal	Clinical n = 10	1.02 (1.06)	3.75 (1.09)	-0.66 (0.87)
		Non-clinical n = 6	3.1(1.37)	5.49 (1.42)	2.11 (1.13)

			Target Type			
			Target-after-Neutral	Target-after-Fear	Target-after-Sad	Target-after-Target
P300	L. Parietal	Clinical n = 10	4.12 (1.19)	5.68 (0.97)	5.5 (1.21)	3.23 (1.31)
		Non-clinical n = 6	4.44 (1.54)	5.5 (1.26)	5.2 (1.56)	5.71 (1.69)

LPP	L. Occipital-Temporal	Clinical n = 10	-0.81 (0.99)	1.85 (0.76)	2.04 (0.99)	-0.75 (0.82)
		Non-clinical n = 6	2.29 (1.28)	3.37 (0.98)	2.03 (1.28)	2.03 (1.28)

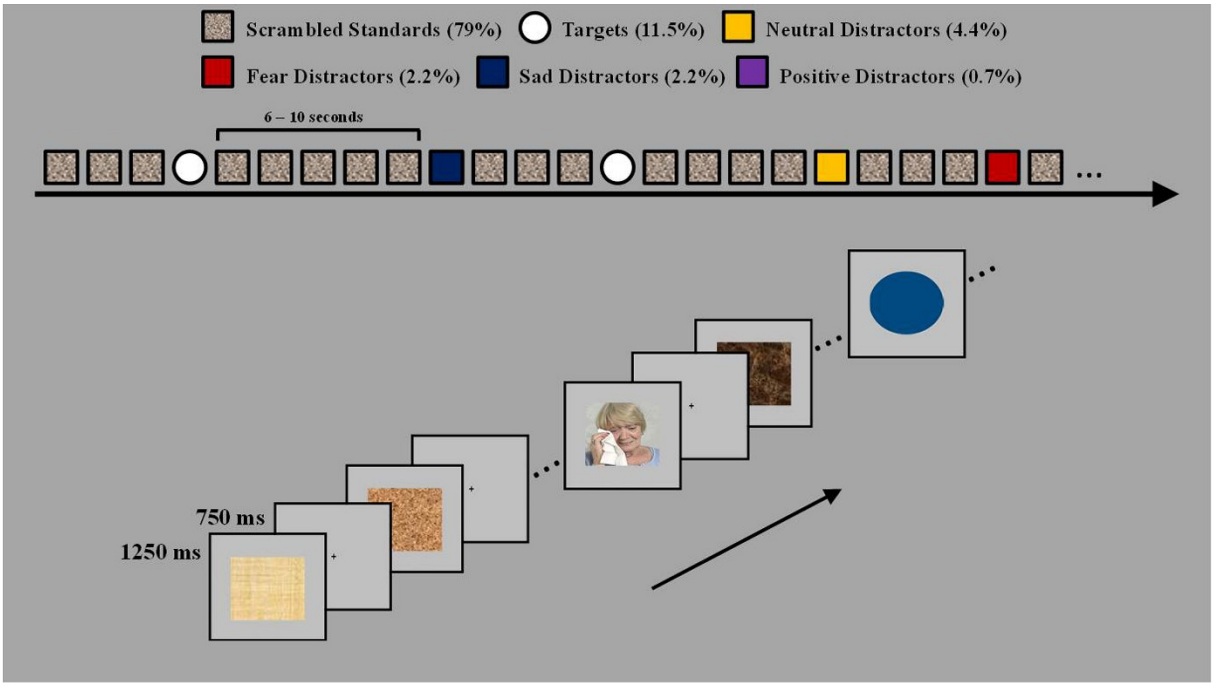

Figure 5-1: Task design. The task used 4 types of rare events, fear, sad, neutral distracters, and target circles varying in size and color). The four types of rare events were presented pseudorandomly between the standard scrambled pictures and were separated by 6 – 10 seconds. Participants were instructed to make a left hand button press to all scrambled pictures and any picture with a person and to make a right hand button press to all target stimuli.

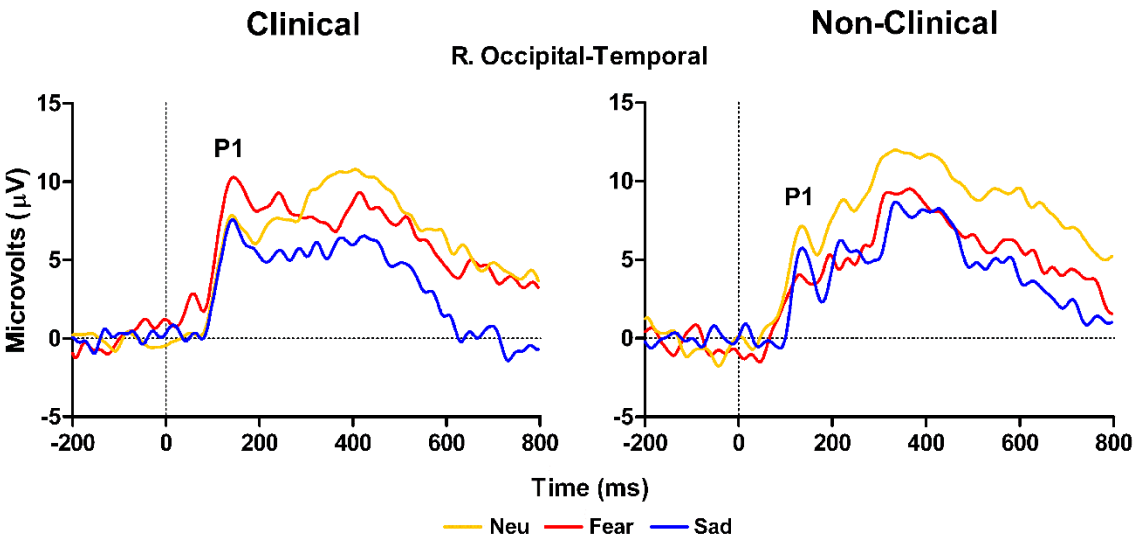

Figure 5-2: Grand average waveforms in response to distracter stimuli over right temporal-occipital electrodes showing larger peak P100 amplitude to fearful distracters compared to neutral and sad distracters for clinical adolescents (left panel) compared to non-clinical adolescents (right panel). Neu = Neutral pictures; Fear = Fear Pictures, Sad = Sad Pictures

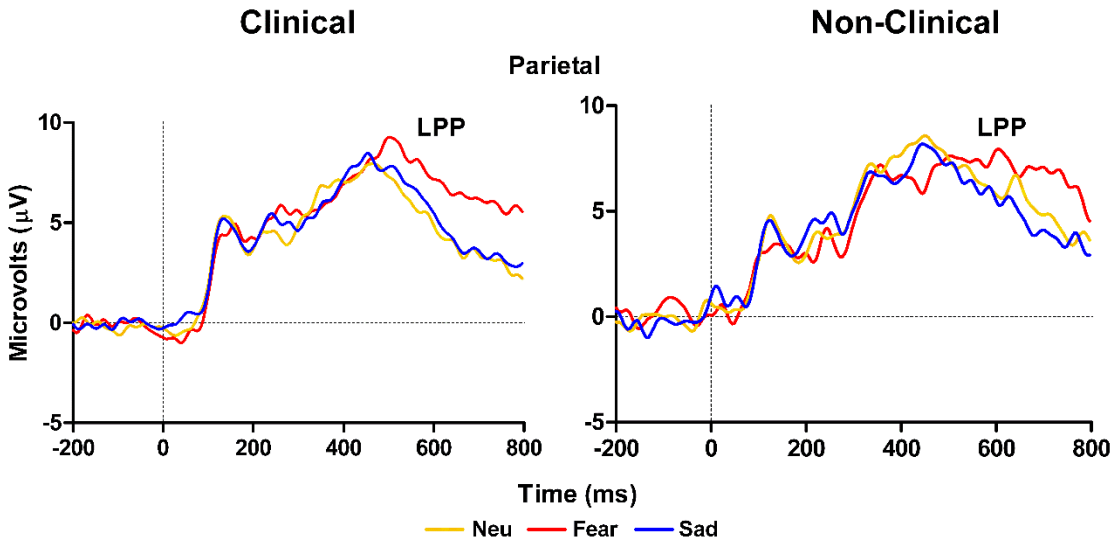

Figure 5-3: Grand average waveforms in response to distracter stimuli. The late positive potential (LPP) over left, midline and right parietal electrodes is larger for fearful distracters compared to neutral and sad distracters for clinical adolescents (left panel), but not non-clinical adolescents (right panel). Neu = Neutral pictures; Fear = Fear Pictures, Sad = Sad Pictures

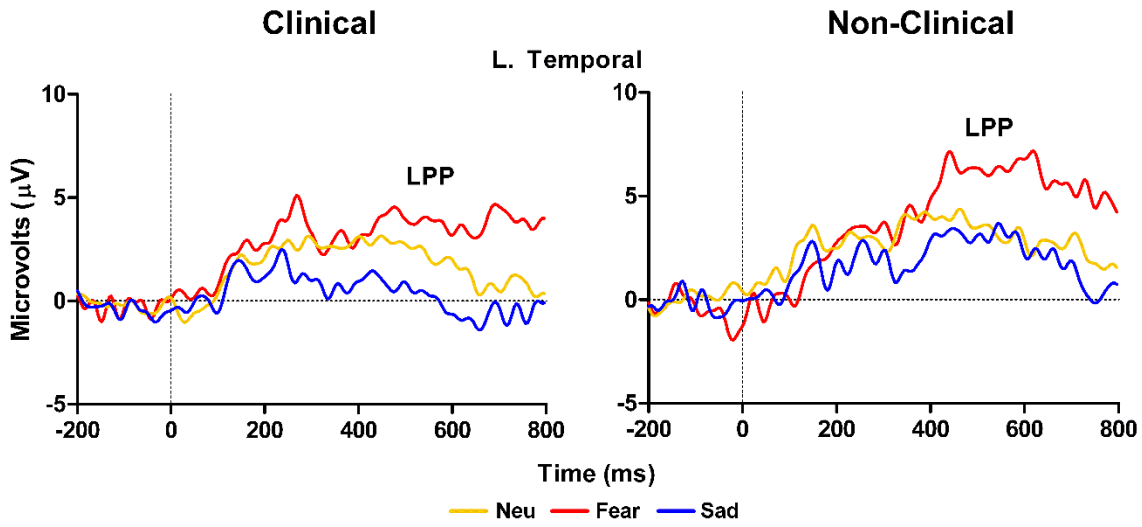

Figure 5-4: Grand average waveforms from left temporal electrodes showing a larger LPP for clinical adolescents in response to high arousal negative fearful distracters compared to neutral distracters. The LPP did not differ between neutral and sad distracters (left panel). Non-clinical adolescents had no significant differences between distracter groups (right panel). Neu = Neutral pictures; Fear = Fear Pictures, Sad = Sad Pictures.

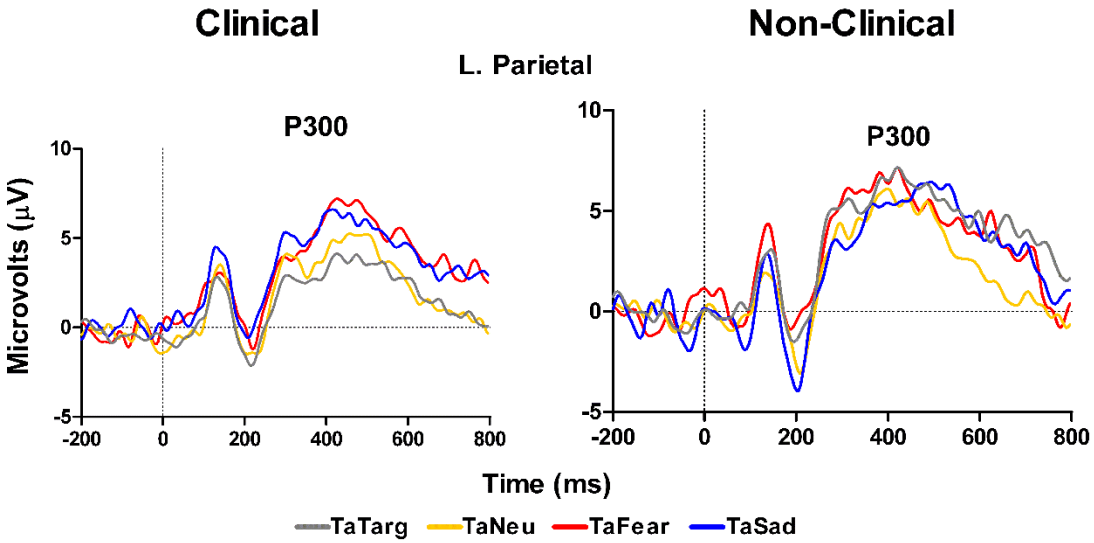

Figure 5-5: Grand average waveforms in response to target stimuli over left hemisphere parietal electrodes. Figure shows increase in P300 amplitude in response to targets-after-sad and targets-after-fear compared to targets-after-targets for the clinical group (left panel), but not in the non-clinical group (right panel). TaTarg = Target-after-Target; TaNeu = Target-after-Neutral; TaFear = Target-after-Fear; TaSad = Target-after-Sad.

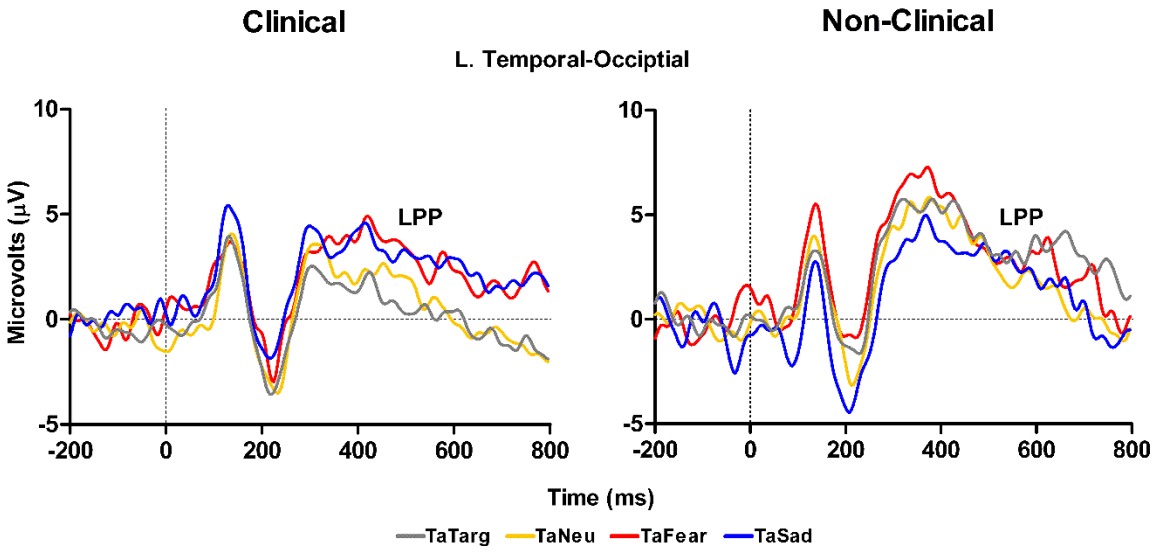

Figure 5-6: Grand average waveforms to target stimuli from left-hemisphere temporal-occipital electrodes show an effect of valence on the LPP in response to target processing with both targets-after-sad and -fear having an increased amplitude compared to targets-after-targets for the clinical (left panel), but not non-clinical (right panel) group. TaTarg = Target-after-Target; TaNeu = Target-after-Neutral; TaFear = Target-after-Fear; TaSad = Target-after-Sad.

CHAPTER 6

NEURAL CORRELATES OF IMPAIRED RESPONSE INHIBTION IN ADOLESCENT PSYCHOPATHOLOGY – FMRI EVIDENCE

Regional and Network Alterations Linked to Impaired Response Inhibition in Adolescent Psychopathology: A Functional Magnetic Resonance Imaging Investigation

A version of this chapter is currently being prepared for peer-reviewed publication

Adolescence is the development period between childhood and young adulthood and is characterized by maturation in many domains [i.e., biological, psychological, sociological (Spear, 2000)]. Adolescence is also a time period marked with increases in risky behaviors (Luna & Sweeney, 2004; Steinberg, 2004). Characterizing impulse control deficits associated with risk-taking behaviors is impaired/reduced response inhibition, a typical phenotype of adolescence. Increased risk-taking behaviors are exacerbated in adolescents with psychopathology (Carli et al., 2014; Kaess et al., 2014; Zhou et al., 2012). The increased risky behavior in adolescent psychopathology, coupled with psychiatric disorders as a leading factor for suicide (Heron, 2013; Moscicki, 2001), make understanding adolescent psychopathology critically important since these individuals are at the greatest risk for adolescent mortality. The overarching goal of the current investigation was to shed light on increased impulse control deficits observed in clinical adolescent populations. Specifically, we examined behavioral differences and their associated neural correlates between adolescents with and without psychopathology in a task requiring effortful goal-oriented attentional control to promote response inhibition of a prepotent response selection.

In the Go/No-Go task, a classic response inhibition paradigm (Donders, 1868), participants are given a stream of stimuli and instructed to make a response for frequent stimulus type and withhold a response for an infrequent stimulus type. Animal research and clinical neuropsychology investigations have shown that successful performance on a response inhibition task (e.g., Go/No-Go) is dependent on frontal lobe functioning (Mesulam, 1985). This earlier work was corroborated and the role of the frontal lobe refined with the advent of functional magnetic resonance imaging (fMRI). Brain imaging data has shown this task to consistently activate frontal cortical areas important for executive functioning [dorso-lateral prefrontal cortex,

(dlPFC), (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002)], motor inhibition [the opercular portion of the inferior frontal gyrus (IFG), (Durston, Thomas, Yang, et al., 2002)], emotion-cognition integration and affective control [anterior cingulate cortex (ACC), (Bush, Luu, & Posner, 2000)]. In addition to the frontal areas engaged, parietal regions shown to be important for attentional control and orienting (Corbetta, Patel, & Shulman, 2008; Corbetta & Shulman, 2002) are also involved in successful task performance (Bunge et al., 2002; Durston, Thomas, Worden, Yang, & Casey, 2002). Behaviorally, impaired response inhibition ability manifest has slowed reaction time (RT) and increased error rates (Durston, Thomas, Yang, et al., 2002). Using a conflict key-pressing/response selection task, decreased accuracy and longer RT were found for trials that required a response incongruent with the prepotent response (Gerardi-Caulton, 2000); this paradigm is very similar to the Go/NoGo, but instead of participants withholding a response (response execution) to an infrequent stimulus they are required to make different response (response selection). Brain imaging research using both response execution and response selection paradigms of inhibition show similar brain-behavior relationships for both paradigms (Casey, Castellanos, et al., 1997). Overlapping behavioral and brain imaging findings from these two slightly different paradigms suggest that they are tapping into similar mechanisms required to engage effortful executive control necessary to perform the task (Rubia et al., 2001).

Research examining the effect of age on this task show that younger individuals perform poorer than adults. Increased error rates (Eigsti et al., 2006) and slowed RT (Liston et al., 2006) are accompanied by decreases in frontostriatal microstructure (Liston et al., 2006), alterations in frontostriatal functional connectivity (Somerville, Hare, & Casey, 2011) and in the PFC activation. Concerning the latter, findings appear to depend on the age range investigated and if

performance on the task implemented is equal across age or is impaired for younger participants. Studies have shown overall decreases in activation (Bunge et al., 2002; Rubia et al., 2000), changes in regional recruitment (Tamm, Menon, & Reiss, 2002), changes in the extent of the recruitment (Casey, Trainor, et al., 1997), or an inverted U-shape pattern of activation from childhood to adulthood (Luna, Padmanabhan, & O'Hearn, 2010; Luna et al., 2001).

Another cognitive process involved in successfully performing response inhibition paradigms is *sustained attention* (Grahn & Manly, 2012). Alterations in attention have long been observed in psychopathology (Rothbart & Posner, 2006). The link between attention and psychopathology, and impulse control and psychopathology make response inhibition paradigms ideal for investigating neural correlates associated with maladaptive alterations in these processes related to the presence of various psychiatric disorders. However, similar to the unclear understanding in the degree and specificity of PFC engagement in response inhibition tasks for adolescents relative to children and adults (Luciana, 2006), research exploring alterations in neural functioning for response inhibition in adolescents with psychiatric disorders also reports inconsistent findings (Deveney et al., 2012; Diler et al., 2014; Diler et al., 2013; Durston et al., 2003; Passarotti, Sweeney, & Pavuluri, 2010; Suskauer et al., 2008). As a result of these discrepancies, general references to abnormal cortical involvement in various adolescent clinical populations (ADHD, OCD, BpD, UD, anxiety) are made.

There are at least five reasons for the lack of consensus concerning neural alterations in response inhibition. In no particular order these are: slight variations in the tasks used, the presence or absence of behavioral findings, low sample size, the disorder studied, and different developmental trajectories for the disorders studied. In regards to the disorder studied, pediatric neuroimaging research has taken an approach to understanding psychopathology largely based

on identifying disorder specific alterations of neural mechanisms. This approach, has increased validity in adult psychopathology where a single psychiatric disorder, or a single grouping of psychiatric symptoms [i.e., internalizing vs. externalizing] can be more easily delineated. However, high co-morbidity for psychiatric disorders is typical of adolescent psychopathology (Knapp & Jensen, 2006). In fact, some clinicians claim that adolescent psychopathology is best described as a constellation of co-occurring disorders (Price & Zwolinski, 2010). Therefore, it may be equally or more advantageous to examine overarching similarities in cognitive processes and their neural correlates impacted in adolescent psychopathology (Sauder, Beauchaine, Gatzke-Kopp, Shannon, & Aylward, 2012; Singhal et al., 2012). Taking this approach to increase our understanding of the neural manifestation of adolescent psychopathology, in conjunction with using a task that behaviorally shows impairment in response inhibition for the clinical group (thus offering increased ecological validity), inherently allows for larger sample sizes and may offer more insight/consensus to what neural regions/networks are impacted. To that end, the current investigation examined neural correlates linked to behavioral impairment in a response selection task in a group of adolescents with Axis-I affective, attentional and behavioral disorders. Moreover, group differences in functional connectivity between regions related task performance and individual differences in attentional control were also examined.

Methods

Participants. Thirty-six [18 clinical (8 male), 18 non-clinical (8 male)] adolescents (12 – 17) years; Mean = 15; SD = 1.5), all right-handed, participated in the study. The clinical adolescents (CAs) were recruited from a residential mental-health treatment facility in the City of Edmonton, Alberta, Canada. These adolescents were clinically diagnosed with diagnostic and statistical manual of mental health disorders 4th edition (DSM-IV) Axis-1 disorders. Due to the large

comorbidity and heterogeneity in our sample's diagnosis we grouped depressive disorders (major depression and dysthymia) and anxiety disorders (generalized anxiety, post-traumatic stress disorder, social phobia) together into one 'distress disorders' category. We also grouped all sub-types of ADHD (combined, predominantly inattentive type, predominantly hyperactive/ impulsivity type) together into one 'ADHD' category. Clinical characteristics are summarized in Table 1. Non-clinical, healthy control adolescents (HCs) recruited from the City of Edmonton, were screened for psychiatric illness and drug/alcohol use with the Mini-international Neuropsychiatric Interview for kids [M.I.N.I-Kid, (Sheehan et al., 1998; Sheehan et al., 2010)]. Healthy controls were matched to CAs on age (within 1 year from time of scanning), sex, and handedness. All participants had normal or corrected-to-normal vision. Informed consent and assent were obtained from parental guardians and adolescents before participating. The experimental protocol was approved for the ethical treatment of human participants by the Health Research Ethics Board at the University of Alberta.

[Insert Table 1 about here]

Test of Variables of Attention (TOVA). To examine group differences in attentional control a continuous performance test was administered. The TOVA is a 21.6 minute long computer task and is a standardized measure of executive attention (Leark, Dupuy, Greenberg, Corman, & Kindschi, 1996). Participants are required to look for and response to target stimuli embedded in a stream of target and non-target stimuli. The TOVA test yields an Attention Performance Index (API). The API is a summation of the z-scores for response time from the first half of the task, D prime from the second half of the task, and response time variability for the entire task (halves 1 and 2).

Task and Stimuli.

Emotional Oddball Task. Participants performed a modified version of the emotional oddball paradigm (Wang, McCarthy, Song, & Labar, 2005). The stimuli and design of the modified emotional oddball task were described in a previous report focusing on event-related potential recordings (Singhal et al., 2012). Briefly, the task contained frequent stimuli serving as the baseline [scrambled pictures, 79% (465 trials)], infrequent oddball distracter and target stimuli, 21% (124 trials). Infrequent oddball distracters consisted of neutral (neu), sad, fearful, and positive pictures. Positive oddball distracters (four in total) served as emotional anchors and were not included in the analysis. To control for visual complexity, sad and fear pictures were paired to a neutral picture that possessed similar visual qualities (e.g., man sitting with a neutral expression vs. man sitting with a sad expression). Infrequent oddball targets were images of a solitary circle. Circles varied in size and color so that each circle was unique. Targets could be sub-grouped according to which type of oddball distracter stimuli they followed [targets-after-neutral (T-A-N), targets-after-fear (T-A-F), targets-after-sad (T-A-S), and targets-after-targets (T-A-T)]. Oddball distracter stimuli were pictures selected from international affective picture database [IAPS, (Lang, Bradley, & Cuthbert, 2008)] based on normative scores for valence and arousal ratings and from in-house pictures used in previous studies (Wang, Krishnan, et al., 2008; Wang, LaBar, et al., 2008; Wang et al., 2005). The mean valence and arousal normative scores as rated by 33 participants (see information on the ratings task below), respectively, were as follows: 5.36/2.36, for Neu; 2.96/3.83, for Sad; and 2.62/5.1, for Fearful. Ratings data from 3 participants were not included due to an error during data collection. Pairwise comparisons found each of the emotional groups were emotionally perceived significantly different. Fear images had higher arousal ratings than sad images which had higher arousal ratings than neutral images,

[$F(2,64) = 52.86$, $p < 0.001$]. For valence, fear images had more negative ratings compared to sad images, which had more negative ratings than neutral images, [$F(2,64) = 138.95$, $p < 0.001$].

The frequent distracter stimuli contained the same spatial frequency and luminance of oddball distracter stimuli as they were digitally scrambled versions the oddball distracters. Each stimulus (frequent and infrequent) was presented for 1250 msec in the center of the screen and was followed by a fixation for 750 msec. The inter-trial interval was 2000 msec and participants had this long to make a response. The inter-rare interval (IRI) between oddball (distracter and target) stimuli was randomized on a negative exponential distribution with a median of 8 sec (range = 6 – 10 sec). Participants were instructed to look for the target stimuli amongst the image stream and make a right hand button press every time they saw a target and a left hand button press to all other pictures. Participants were also instructed to respond as accurately and quickly as possible to all stimulus types, and to experience any thoughts or feelings the pictures may trigger.

Ratings Task. All oddball distracter stimuli were re-presented to the participants after the completion of the emotional oddball task to obtain valence and arousal ratings. Each picture was presented in the center of the screen and the self-assessment manikin (SAM) scale for either valence (1 = negative to 9 = positive) or arousal (1 = no arousal to 9 = high arousal) was presented at the bottom of the screen (Lang, 1980). After a response was made for one ratings scale the other scale appeared in its place. The picture was displayed until the participant made a response for both valence and arousal scales. Participants were instructed to respond quickly and not think too much about each picture so as to provide their initial, automatic reaction to the pictures.

Procedure. The oddball trials (124) were divided into 5 runs, each lasting 4 minutes and 20 seconds. To avoid induction of a negative mood state, oddball distracter stimuli were pseudo-randomized to prevent more than two negative distracter trials from appearing in a row. Following participant set-up, localizer and MPRAGE acquisition, participants were re-given task instructions and the 5 functional runs were collected. Data collection for the present study was part of a larger investigation examining a non-pharmacological approach to treating youth with mental health disorders. Briefly, this larger investigation explored the effects of mindfulness based stress reduction therapy in a clinical youth population using brain, behavior and qualitative assessments. Of the clinical adolescents who participated in the baseline neuroimaging portion of this larger investigation, a sub-set of 18 were selected has they qualified as matches for the non-clinical adolescents who participated. The baseline session for the larger investigation involved a day-long testing session for the clinical adolescents soon after they were admitted to the residential treatment facility. The baseline testing session involved participants completing questionnaires, tasks on a computer, and another neuroimaging session in which electroencephalogram was acquired. Importantly, the sequence of events comprising the baseline testing session was kept the same for the clinical and non-clinical participants. Participants viewed pictures outside the MRI task during the day-long testing session. As such, the ratings task included all pictures viewed during the entire day and was performed at the very end of the testing session. The TOVA was administered during an early testing session. For HCs, this occurred during the pre-screening session with the M.I.N.I-Kid. For CAs, this occurred during an earlier and largely questionnaire-based testing session that took place at the in-house residential treatment facility.

Imaging Protocol. MRI scanning was conducted on a 1.5T Siemens Sonata scanner. First, a sagittal localizer and 3-D magnetization prepared rapid acquisition gradient echo anatomical (MPRAGE) series are acquired [MPRAGE; field of view = 256 x 256 mm, repetition time (TR) = 1600 msec, echo time (TE) = 3.82 msec, flip angle (FA) = 15°, number of slices = 112, voxel size = 1 mm^3]. Then gradient echoplanar imaging (EPI), allowing for full-brain coverage collected axially, was used for the acquisition of the functional volumes (EPI; field of view = 256 x 256 mm, TR = 2000 msec, TE = 40 msec, FA = 90°, number of slices = 28, voxel size = 64 mm^3].

Behavioral Data Analysis. To examine group differences in executive attention ability controlling for age a multiple regression with Group and Age entered as independent variables was performed on the attentional performance index scores obtained from the TOVA. To examine group differences in task performance as a function the preceding distracter type, a mixed-model ANCOVA was performed on accuracy data with the within-subjects variable target type, with four levels (T-A-T, T-A-N, T-A-F, T-A-S); the between-subjects variable group, and age as the covariate. Due to significantly different regression slopes between groups in the relationship between age and distracter and target RT, task performance was directly assessed in the current investigation using accuracy data. Since the ANCOVA analysis examining target accuracy only showed a main effect of group on overall task performance all target types were collapsed for subsequent behavioral and brain imaging analyses. To determine if the relationships between attentional control, target accuracy and target RT differed across groups, partial correlations between these three variables were performed for each group separately with the effects due to age removed. Where appropriate, differences between groups in Pearson r

coefficients were then assessed by conversion to Fisher's Z (Fisher, 1921) followed by the calculation of a z-test statistic.

fMRI Data Analysis. Imaging data analyses were performed on all 36 participants (18 HC, 18 CA), using SPM5 in conjunction with in-house custom Matlab scripts. Statistical analyses were preceded by the following preprocessing steps: quality assurance, TR alignment, motion correction, normalization, and smoothing (8^3 mm kernel). For individual analyses, task-related activity was identified by convolving a vector of the onset times of the stimuli with a synthetic hemodynamic response and its temporal derivative. The general linear model, as implemented in SPM5, was used to model the effects of interests and other confounding effects (e.g., session effects, magnetic field drift). Group-level brain imaging analyses paralleled the behavioral analyses to examine group differences in target processing. Furthermore, similarities and differences between groups in brain-behavior relationships were examined. Lastly, group differences in neural response linked to overall differences in target accuracy and to more subtle differences in brain-behavior relationships were further examined with functional connectivity to elucidate potential dysfunction in overarching networks between groups. Specific imaging analyses performed to address each of these are described in detail below.

Neural correlates associated with differences in behavior.

To examine brain activity linked to the decreased target accuracy observed in clinical adolescents we generated contrasts representing brain activity to all targets relative to baseline (regardless of target type) for each group separately. Between group differences in target-related activity was then assessed by a two-sample t-test with age as a covariate. To ensure that group differences were driven by an increase in brain activity in response to targets relative to baseline, conjunction maps were created where each group comparison was inclusively masked by a main

effect of target relative to baseline for the group showing greater activity [i.e., (HC – CA) ∩ HC; (CA - HC) ∩ CA]. Next we wanted to examine whether areas identified by the above conjunction maps were part of an overall goal-oriented, target processing network or part of an overall distracter processing network. To do this we created group specific contrasts for target greater than distracter activity and vice-versa. Cortical regions for this analysis were identified with $p \leq 0.001$, while subcortical structures such as the amygdala, hippocampus, parahippocampus, thalamus and striatal regions were identified with $p \leq 0.05$. These contrasts were then used as inclusive masks to categorize areas showing group differences in target-related activity into those linked to goal-oriented attention vs. general distracter/perceptual processing [e.g., (HC – CA) ∩ (HC Targets > HC Baseline) ∩ (HC Targets > HC > Distracters)]. Whole brain group comparisons were made using a p-value of 0.05 and an extent threshold of 10 voxels for cortical areas and 5 voxels for subcortical areas. Masks consisting of within group t-test for differences (e.g., Targets > Baseline, Targets > Distracters) were made with a p-value of 0.005. Thus, the combined probability of the conjunction maps (0.05 x 0.005) was less than 0.001 (Fisher, 1950).

Differences in brain-behavior relationships.

To examine brain-behavior relationships paralleling the relationship between attentional control and target RT identified in the behavioral data, correlation maps were created between the brain activity in response to targets and target RT, accuracy and attentional control for each group separately. All correlation maps controlled for any effects due to age. To identify areas linked to the relationship identified in the behavioral data two double conjunction correlation maps were created using the individual correlation maps between brain activity to targets and target RT, and brain activity to targets and attentional control score. One of the double

conjunction maps examined areas of overlap for a positive relationship between brain activity to targets and attentional control, and a negative relationship between brain activity to targets and target RT. That is, the overlap in brain regions showing increased neural engagement linked to attentional control and faster RT. The other double conjunction map examined areas of overlap for a negative relationship between brain activity to targets and attentional control, and a positive relationship between brain activity to targets and target RT. That is, the overlap in brain regions showing increased neural engagement linked to decreased attentional control and slower target RTs. This was done for each group separately.

To identify additional relationships between brain activity to targets and task performance double conjunction correlation maps were also created using individual correlation maps examining the relationship between target activity and target RT, and target activity and accuracy. That is, the overlap in brain regions showing increased neural engagement linked to increased accuracy for, and faster RT to targets. Due to the large role frontal and parietal regions play in executive functioning (Corbetta & Shulman, 2002; Hopfinger, Buonocore, & Mangun, 2000; Luciana, 2006; Luna, Garver, Urban, Lazar, & Sweeney, 2004) and research showing their dysfunction associated with adult psychopathology (Denkova et al., 2010; Morey et al., 2009; Morey et al., 2011; Ritchey, Dolcos, Eddington, Strauman, & Cabeza, 2011; Wang, Krishnan, et al., 2008; Wang, LaBar, et al., 2008; Warren et al., 2013), alterations in these regions were the focus of the brain-behavior analyses. However, all regions identified, regardless of location are reported in the corresponding tables. Correlation maps were made using a p-value of 0.05 and an extent threshold of 5 voxels. Therefore, the combined probability of the double conjunction maps was 0.0025.

Exploratory analysis examining group differences in functional network connectivity.

Seed ROIs for the exploratory functional connectivity analysis were selected from differences in activity identified in frontal and parietal regions as these regions have significant involvement in executive functioning and show susceptibility to altered functioning associated adult psychopathology (Corbetta & Shulman, 2002; Denkova et al., 2010; Hopfinger et al., 2000; Luciana, 2006; Morey et al., 2009; Morey et al., 2011; Ritchey et al., 2011; Wang, Krishnan, et al., 2008; Wang, LaBar, et al., 2008; Warren et al., 2013). Bilateral dlPFC and LPC regions identified in the analysis examining group differences in response to targets were used as seeds for functional connectivity to determine if these regions were 1) part of the same functional network whose time-series correlated indicating synchronous neural response; and 2) if the overall group differences showing decreased engagement by way of mean activity in these regions for CAs were also associated with decreases in synchronicity. In addition, frontal and parietal areas of activity paralleling relationships in the behavioral data were also used as seeds for functional connectivity. This was done to 1) identify functional networks linked to behavioral relationships identifying improved and impaired attentional control and task performance; and 2) examine group differences in these functional networks.

Three seed ROIs were identified in HCs and one in CAs, showing a link between brain activity to targets and increases in attentional control or accuracy coupled with decreases in RT, as follows. HCs: the right superior frontal gyrus (SFG, BA 6), the ventral anterior cingulate cortex (vACC, BA 32), and the superior parietal lobe (SPL, BA 7); CAs: the left supramarginal gyrus (SMG). Two seed ROIs were identified in HCs and ten in CAs, linking brain activity to targets and decreases in attentional control coupled with increases in RT, as follows. HCs: left anterior SFG (aSFG) and left inferior parietal lobe (IPL); CAs: bilateral SFG and middle frontal

gyrus (MFG), right inferior frontal gyrus (IFG), left ventro-medial prefrontal cortex (vmPFC) and medial frontal cortex, right vACC/SFG, left IPL and right precuneus.

Seed ROIs consisted of the entire cluster that was identified from the preceding analyses. Functional connectivity maps were created by performing an additional analysis based on activity in each individual trial (Rissman, Gazzaley, & D'Esposito, 2004; St Jacques, Dolcos, & Cabeza, 2009). First, parameter estimates were obtained for each trial for each participant by implementing a GLM for first-level analysis where each trial was modeled by a separate covariate. Functional connectivity maps for each participant for conditions of interests were then created by correlating seed ROIs with parameter estimates for each trial included in the conditions of interests. Across group differences in functional connectivity were then determined by performing a two-sample t-test with age as a covariate. Statistical t-maps comparing functional connectivity across groups for each seed ROI were created using a p of 0.05 for cortical and subcortical areas. Performing functional connectivity analysis with multiple seeds allows for a more detailed profile of functional networks associated with a particular cognitive process involved a task (Dwyer et al., 2014). Since we identified multiple seeds for each analysis (with the exception of the brain-behavior analysis investigating areas related to increased attentional control and task performance), we wanted to determine converging areas of connectivity for seeds identified from the same analysis. This approach adds increased specificity of functional networks whose engagement are important for and related to behavioral measures. Therefore, overlapping areas of activity between seeds regions were investigated. To examine overlapping areas of functional connectivity between seed regions, conjunction maps were created using t-maps showing either increased functional connectivity for HC compared to CA or vice-versa. Finally, to determine whether the areas identified by these functional

connectivity analyses were involved in the overall response to target or distracter processing, these conjunction maps were then masked by the corresponding within group difference for general target (Targets > Distracters) or distracter (Distracter > Target) processing. These mask images were implemented using a p of 0.05 for cortical and subcortical areas. Thus, the joint probability of the resulting maps ranged from a p-value of 0.0025 for a double conjunction map to a p-value of 0.00000625 for a quadruple conjunction map.

Results

Clinical Adolescents show impaired task performance and decreased attentional control. To determine group differences in task performance mean target accuracy for each target type was entered into a mixed-model ANCOVA with age as a covariate. A main effect of group was found, showing reduced target accuracy for CA, [$F(1, 33) = 4.29$, $p = 0.046$], see Figure 1A. There was no main effect of target type, or an interaction between target type and group. A regression was performed to examine group differences in attentional control while controlling for age-related effects. The overall regression model was significant and showed that CA had reduced API scores compared to HC, [$F(2, 33) = 3.29$, $p = 0.05$], with group being the only significant contributor to the model, [$t(33) = -2.5$, $p = 0.017$] (see Figure 1B). To examine the relationship between attentional control and task performance, partial correlations, removing any age-related effects, were performed between API score, target RT and accuracy for each group separately. Decreased RT was linked to increased attentional control for both HC and CA, but was only significant for CA [HC, $r = -0.413$, $p = 0.09$; CA, $r = -0.73$, $p = 0.001$]. No other relationships between attentional control, target RT and accuracy were significant (see Figure 1C).

[Insert Figure 1 about here]

Group differences in task performance linked to decreased activity in executive and perceptual processing regions. To examine brain activity linked to the group differences in target accuracy, we compared brain activity to targets for HC versus CA and inclusively masked this comparison by brain activity to targets versus baseline for each group separately. In order to separate differences in activity linked to the engagement of regions of involved in goal-oriented attention vs. those involved in general distracter processing, we also masked this conjunction map by a contrast identifying regions where target processing was greater than distracter processing and vice-versa. This was done separately for each group. The comparison examining regions associated with goal-oriented target processing where CAs showed reduced activity, identified bilateral dlPFC (MFG BA 9, SFG, BA 9) and bilateral LPC (bilateral IPL BA 40, left postcentral gyrus BA 2/3) (see Figure 2 and Table 2). The comparison assessing reduced response to targets for CAs in areas associated more with general distracter/perceptual processing compared to HCs identified bilateral temporal-occipital cortex (TOC) and parahippocampus (PHC), see Table 2. There were no cortical areas where activity in response to targets was greater in CA compared to HC. However, the thalamus had increased response to targets in CA compared to HC.

[Insert Table 2 and Figure 2 about here]

Dissociation in ventral medial PFC activity linked to the behavioral relationship between attentional control and target RT. Brain-behavior correlations were performed to identify areas paralleling the relationship between attentional control and target RT observed in the behavioral data. Four conjunction maps were created, two for each group separately. One conjunction map combined correlations maps for a positive covariation between attentional control and brain activity in response to targets, and a negative covariation between target RT and brain activity to targets. The other conjunction map combined correlation maps for a negative covariation

between brain activity in response to targets and attentional control, and a positive covariation between brain activity to targets and target RT. Frontal regions identified in HCs showing increased brain activity coupled with increased attentional control and faster RT included a cognitive control region [right dlPFC, SFG BA 6] and an emotion-cognition integration region (right vACC BA 32), see Table 3. In CAs left vmPFC (BA 10) and right vACC (BA 32/10) were identified as having increased engagement linked to decreased attentional control and increased target RT. Thus, a dissociation was found between groups in ventral medial PFC activity to targets, attentional control and task performance with vACC related to improvement in HCs, and vACC/vmPFC related to impairment in CAs, see Figure 3. Other regions related to impairment in CAs included a number of frontal regions involved in cognitive control (bilateral MFG, dorsal medial frontal cortex), motor (SFG BA 8), and emotion (right IFG BA 47) processing, as well as a parietal attentional region (left IPL BA 40), see Table 3.

Increased attentional control and task performance in CAs was related to increased engagement of a parietal attentional region (left SMG), see Table 3. When examining the opposite relationship between brain activity, attentional control and RT (with increased engagement during target processing linked to decreased attentional control and task performance), a frontal cognitive control region (left SFG BA 10), an emotion-cognition integration region (right dACC BA 32), and a parietal attention region (left IPL BA 40) were identified in HCs (see Table 3). Brain-behavior correlations targeting areas of activation associated with increases in task performance via increased accuracy and faster RT identified a parietal attention region (right SPL BA 7) in HCs. No areas were identified meeting the criteria in CAs.

[Insert Table 3 and Figure 3 about here]

Increased task-related functional connectivity between fronto-parietal-striatal regions for HCs versus vmPFC-MTL regions for CAs. Exploratory functional connectivity analysis using the seeds located in bilateral MFG and IPL identified when examining general group differences in target processing showed these seed regions to also be part of the same functionally connected network. Common areas of increased functional connectivity were found in dorsal frontal, parietal and striatal areas between three of four seed regions for HCs compared to CAs, see Table 4. Functional connectivity of the right and left MFG, and left IPL had a large degree of overlap in bilateral MFG, SFG, IPL and caudate, and left postcentral gyrus, see Figure 4. In addition, bilateral MFG had increased connectivity with the cingulate cortex and midline parietal areas (precuneus) whereas the IPL seeds did not.

[Insert Table 4 and Figure 4 about here]

Exploratory functional connectivity analyses using seeds identified from analyses examining brain-behavioral relationships in HC's related to improved attentional control and task performance showed increased functional connectivity compared to CAs in cognitive control areas (bilateral MFG and lateral parietal cortex, and right cingulate cortex). Increased connectivity with these seed regions for HC's was also identified in motor areas (right postcentral gyrus) and posterior insula (see Table 5). No areas were observed where CAs had greater functional connectivity than HCs when using these seeds regions. For HCs, seed ROIs associated with impaired attentional control and task performance had greater functional connectivity in midline parietal regions and medial frontal cortex (see Table 5).

[Insert Table 5 about here]

As mentioned above, the vACC was associated with enhanced performance and increased functional connectivity with cognitive control regions for HCs. Similar, but non-overlapping areas (see Figure 3), in CA's were related to reduced attentional control and task performance (vmPFC and vACC). These areas showed increased functional connectivity with medial temporal lobe regions involved in distracter processing, see Figure 4 and Table 6. Whereas these same seed regions (i.e., vmPFC and vACC) showed greater functionally connectivity for HCs in dorsal frontal and parietal regions, see Table 7. In CAs, only one seed (L. SMG) ROI was identified when examining the brain-behavior relationship linked to improved attentional control and task performance. Therefore, areas of overlap for greater functional connectivity could not be assessed. However, bilateral MFG (BA 9) and right cingulate cortex (BA 32) were identified has having greater synchronous activity compared to HCs for this single seed region, see Table 6. The reverse contrast for this seed region showed a number of areas with greater functional connectivity for HCs, see Table 7. Some of these included cognitive and emotional control regions [i.e., bilateral dlPFC (MFG BA 6, 10, 46), left vlPFC (IFG BA 45), bilateral cingulate cortex (BA 24, 32), and bilateral LPC (IPL BA 40, SPL BA 7)].

[Insert Tables 6, and 7 about here]

Discussion

The current investigation examined differences in goal-oriented processing related to successful response inhibition between adolescents with and without Axis-I affective, attentional and behavioral disorders. This study yielded three main findings. First, decreased attentional control and impaired task performance in CAs was associated with decreased engagement of dorsal frontal and parietal cognitive control regions. Second, a dissociation was found in vACC

between groups in the relationship of the engagement of this region during target processing and individual differences in attentional control and task performance. HC participants that had higher attentional control scores and faster RTs to targets exhibited increased vACC engagement during target processing. Alternatively, CA participants that had decreased attentional control scores and slower target RTs exhibited increased vACC/vmPFC engagement during target processing. Third, functional connectivity analysis revealed that the decreased engagement of frontal and parietal cognitive control regions identified when assessing mean target activity for CAs were also associated with decreased functional connectivity compared to their HC counterparts. Furthermore, and extending our understanding of the dissociation in the vACC, functional connectivity analysis revealed for CAs this region had greater connectivity with MTL regions, whereas for HCs this region had greater connectivity with frontal and parietal cognitive control regions. These main findings are discussed, in turn, below.

Group differences in task performance linked to decreased activity in executive and perceptual processing regions. Our behavioral results showing impaired response inhibition in our clinical adolescent group replicates countless of prior studies examining response inhibition in specific psychiatric disorders in adolescence, thus paralleling the impulse control problem these individuals have relative to their healthy counterparts in real world settings. Our brain imaging results are in agreement with earlier studies showing overall decreases in PFC engagement. In the presence of clear behavioral impairment in task performance and attentional controls scores we found no cortical areas showing increased activation in CAs. Areas that were the most impacted in CAs were bilateral dlPFC (MFG, BA 9) and LPC (IPL, BA 40), and left postcentral gyrus. Interestingly, we did not find group differences in vlPFC (IFG, BA 44). This area is important for inhibiting motor programs already activated. The absence of a difference in

this area may reflect the fact that we were performing a response selection task, which required the inhibition of a prepotent response and execution of an alternate response rather than a task requiring complete inhibition of responses. Another possibility is that impairment in task performance wasn't the result of differences in the ability to inhibit an action, but was more related to the inability to maintain attention (goal-oriented and/or sustained attention) throughout the task. Involvement of dorsal PFC and LPC may be more indicative of the latter option, although these possibilities are not mutually exclusive.

Dissociation in ventral medial PFC activity linked to the behavioral relationship between attentional control and target RT. Investigation of brain-behavior relationships paralleling the relationship between individual differences in attentional control and task performance in the behavioral data, identified frontal (R. SFG and vACC) regions in HCs and a parietal (L. SMG) region in CAs. These regions showed increased engagement during target processing related to increased attentional control scores and faster target RT. In HCs, increased activation of parietal region (R. SPL) was related to increased accuracy and faster RT. In CAs, there were no areas related to target accuracy and RT. Involvement of frontal and parietal regions was not unique to this favorable relationship between brain activity and behavior. When looking at the opposite relationship between these behavioral measures and neural engagement during target processing, different areas of frontal cortex (L. SFG, R. dACC) were identified and one parietal region (L. IPL) in HCs. In CAs, the opposite relationship was identified in frontal regions (lateral MFG and IFG, and dorsal and ventral medial frontal gyrus and SFG, and ventral ACC) and one parietal region (IPL). Engagement of these regions was related to lower attentional control scores and slower RT. That is, these regions were 'offline' or less involved for individuals with high attentional control scores and faster RT. In CAs many more frontal areas were related to

decreases in attentional control scores and slower RT. This may reflect increased neural resources are necessary to perform the task for individuals' low attentional control. Alternatively, this may be an artifact of including all trials (regardless of correct or incorrect) in the brain imaging analysis and brain activity from incorrect trials is driving this relationship. However, the behavioral data suggest that this is unlikely as most incorrect responses made by CAs resulted from a failure to inhibit the prepotent response and therefore resulted in faster RT compared to correct trials. Therefore, activity associated with incorrect trials would correlate with faster, not slower RT.

Importantly, this analysis identified a dissociation in vACC/vmPFC between groups in the relationship of the engagement of this region during target processing and individual differences in attentional control and task performance. HC participants that had higher attentional control scores and faster RTs to targets exhibited increased vACC engagement during target processing. Whereas, CA participants that had decreased attentional control scores and slower target RTs exhibited increased vACC/vmPFC engagement during target processing. Previous research has shown altered engagement of this region for clinical relative to non-clinical adolescent populations. Our results did not show group differences in mean activity for this region, but are consistent with reports showing increased ventral/rostral ACC activity with a number of impairments, from severity of symptoms and error-related activity in OCD (Fitzgerald et al., 2005) to increased errors in individuals with a SERT polymorphism associated with increased risk for MDD (Holmes, Bogdan, & Pizzagalli, 2010). However, unlike in these reports, our results show an opposing relationship between clinical and healthy adolescents, implicating involvement in different networks between groups (one linked to task enhancement in HCs and

the other to task impairment in CAs), which was confirmed in our exploratory functional connectivity analysis discussed below.

Increased task-related functional connectivity between fronto-parietal-striatal regions for HCs versus vmPFC-MTL regions for CAs. Exploratory functional connectivity analysis revealed that the decreased engagement of frontal and parietal cognitive/attentional control regions identified when assessing mean target activity for CAs were also associated with decreased synchronous behavior compared to their HC counterparts. In addition to these cortical regions, the caudate nucleus also showed decreased connectivity. Previous research has pointed to impairments in response inhibition linked to alterations in a cingulo-frontal-parietal attention network (Bush, 2011), cortical-striatial-thalamic-cortical circuits (van Velzen, Vriend, de Wit, & van den Heuvel, 2014) and a ventrolateral frontostriatal network (Giedd et al., 1999; Luna et al., 2001; Somerville et al., 2011). Here we show impairment in a network of regions located dorsally in the striatum, cingulate and lateral prefrontal and parietal cortices. Our findings are not inconsistent with research showing alteraltions in a ventrolateral frontostriatal network as many of the response inhibition paradigms showing this incorporated a motivation factor where there was none here and therefore ventral lateral orbitofrontal areas linked to motivation processes were not needed.

Expanding our understanding of the role of vACC in response inhibition in adolescent psychopathology, we found this region to be part of one of two networks. For CAs, this region had greater connectivity with MTL regions (amygdala, hippocampus, and parahippocampus) that were also engaged during distracter processing. For HCs this region, along with R. SFG and SPL seeds linked to increased attentional control and task performance had greater connectivity with frontal (bilateral MFG), parietal (bilateral) and cingulate cognitive control regions. The

vACC/vmPFC has strong anatomical and functional connections with the amygdala (Kim et al., 2011; Kim & Whalen, 2009) and mature circuitry is associated with one's ability to appropriately regulate emotion where vACC/vmPFC is important for down-regulation of amygdalar response (Gabard-Durnam et al., 2014; D. G. Gee, Humphreys, et al., 2013). Immature circuitry between amygdala and vACC/vmPFC involves increased amygdalar response positively coupled with vACC/vmPFC activity (D. G. Gee, Gabard-Durnam, et al., 2013; D.G. Gee et al., 2014; D. G. Gee, Humphreys, et al., 2013). In the context of these findings the increased task positive connectivity between these regions for CAs suggest an immature vACC/vmPFC-AMY circuitry that results in an impairment in target processing and response inhibition. The paradigm used in the current investigation may have been key for identifying alterations in this circuitry between groups as its activation may have occurred as a result of processing the oddball distracters items that sometimes preceded the targets. Alternatively, this circuitry could be perpetually activated in CAs. Future work will need to examine differences in task vs. rest-related vACC/vmPFC-AMY coupling between healthy and clinical adolescents to determine if impairment in goal-oriented processing and response inhibition is related to increased sensitivity of this maladaptive circuitry to be engaged (i.e., it's reactivity), or it is related to more enduring differences occurring in the network at rest (i.e., elevated baseline).

Limitations. The inability to control for type of medication or medication duration is a potential confound in the current investigation, but was an unavoidable property of working with this population as many of the CAs were prescribed psychotropic medication before they were admitted to the residential facility. Although this is not ideal for investigations of alterations in neural mechanisms linked to psychopathology, behavioral impairments in response inhibition remained suggesting maladaptive alterations in brain functioning also persisted.

Conclusions

In summary, this study identified brain regions and functional networks associated with impaired response inhibition in adolescent with Axis-I affective, attentional and behavioral mental health disorders. First, we found that the clinical adolescents had overall decreased engagement to targets in frontal and parietal brain regions important in cognitive control. Second, we found a dissociation between clinical and healthy groups in the relationship between vACC activity and individual differences in attentional control and task performance. For the clinical adolescents, increased vACC engagement was related to decreased attentional control and impaired task performance. For the healthy adolescents, increased vACC engagement was related to increased attentional control and enhanced task performance. Third, we identified differences in task-related functional connectivity between groups such that the clinical group had increased vmPFC-MTL coupling and the healthy group had increased frontal-parietal-striatal coupling during target processing. Taken together, these findings shed light on the neural mechanisms related to adolescent psychopathology.

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Table 6-1. Diagnostic and medication in formation for the 18 clinical adolescents.

Diagnosis	**Number**	**Medication (number of patients)**				
	(M/F)	**Unknown/ None**	**Stimulants**	**Anti-depressants**	**Anti-psychotics**	**Other**
Distress disorders *(MDD, Dysthymia, SP, GAD, PTSD)* co-morbid with one or more following disorders						
Distress disorders and ADHD, PCRP	(2/4)	1/-	4	5 - SSRI	2	-
ADHD, CD, ODD, PCRP, RAD	(4/2)	-/-	2	3 – SSRI	3	1 - BZD
ADHD co-morbid with one or more following disorders						
CD, ODD, PCRP, RAD	(2/1)	-/-	1	2 – SSRI	5	-
Others: one or more following disorders						
ODD, PCRP, AD	3 (0/3)	-/2	-	1-SSRI	1	-
Total	18 (8/10)	1/2	8	11 – SSRI	11	1 - BZD

AD = Attachment Disorder; ADHD=attention-deficit/Hyperactivity disorder; CD = Conduct Disorder; GAD = Generalized Anxiety Disorder; MDD = Major Depressive Disorder; PTSD = Post Traumatic Stress Disorder; ODD= Oppositional Defiant Disorder, PCRP=Parent-Child Relational Problem; RAD = Reactive Attachment Disorder; SP = Social Phobia; SSRI, selective serotonin reuptake inhibitor; BZD, benzodiazepine.

Table 6-2. Brain regions showing increased response to targets for HCs compared to CAs (top) and for CAs compared to HCs (bottom).

Brain Regions		Hemi.	BA	Talairach Coordinates x	y	z	T-Value	Cluster Size
[HC Targets > CA Targets] inclusively masked with [HC Targets > Baseline] and [HC Targets > Distracters]								
Cortical							(HC > CA)	
dlPFC	Middle Frontal Gyrus*	L	9	-31	33	39	2.59	11
		R	9	28	40	34	3.12	48
	Superior Frontal Gyrus	R	9	17	49	24		
LPC	Postcentral Gyrus	L	2/3	-50	-21	45	3.09	50
	Inferior Parietal Lobe*	L	40	-46	-42	36	2.28	26
		R	40	58	-38	27	3.4	24
			40	32	-36	41		
Cerebellum								
Anterior Lobe	Culmen	L		-1	-53	-8	2.84	44
		R		6	-56	-15	3.29	
[HC Targets > CA Targets] inclusively masked with [HC Targets > Baseline] and [HC Distracters > Targets]								
Cortical								
TOC	Fusiform Gyrus	L	37	-42	-49	-8	2.36	37
	Middle Temporal Gyrus	L	37	-42	-62	1	3.15	
		R	37	43	-62	-1	2.42	13
			39	43	-72	23	3.15	19
	Middle Occipital Gyrus	R	19	32	-75	21		
Subcortical								
MTL	Uncus	L	34	-16	-7	-22	2.33	13
	Parahippocampal Cortex	L	35	-27	-26	-13	3.13	5
		R	35	21	-34	-9	2.34	9
Cerebellum								
Posterior Lobe	Declive	L		-20	-53	-12		25
Anterior Lobe	Culmen	L		-19	-37	-18		
[CA Targets > HC Targets] inclusively masked with [CA Targets > Baseline] and [CA Targets > Distracters]								
Subcortical							(CA > HC)	
Thalamus	Thalamus	R		10	-11	18	2.16	5

The displayed t-values correspond to peak voxels from the contrast assessing group differences in activation [i.e., (HC Targets > CA Targets) – top, and (CA Targets > HC Targets) - bottom]. Individual maps were created with a p-value of 0.05. Thus the conjunction map had a joint threshold of $p \leq 0.000125$. Asterisks indicate cluster(s) also served as seed region for functional connectivity analysis. BA, Brodmann area; L, left; R, right; HC, healthy control; CA, clinical adolescent; dlPFC, dorso-lateral prefrontal cortex; LPC, lateral parietal cortex; TOC, temporal-occipital cortex; MTL, medial temporal lobe.

Table 6-3. Brain regions showing a relationship with attentional control and task performance.

Brain Regions		Hemi.	BA	Talairach Coordinates x	y	z	T-Value	Cluster Size
Regions associated with increased attentional control and enhanced task performance								
[HC Targets + API] inclusively masked with [HC Targets – Target RT]								
Cortical							+API/-RT	
dlPFC	Superior Frontal Gyrus*	R	6	24	13	49	2.22/1.85	5
vlPFC	Inferior Frontal Gyrus	L	47	-30	8	-17	3.68/2.04	7
MC	Ventral Anterior Cingulate*	R	32	6	43	12	3.03/2.35	6
FC	Precentral Gyrus	R	4	28	-29	49	2.55/1.95	7
[CA Targets + API] inclusively masked with [CA Targets – Target RT]								
Cortical								
dlPFC	Middle Frontal Gyrus - WM	R	6	25	22	32	2.43/	12
FC	Precentral Gyrus – WM	L	6	-38	-11	28	2.27/	22
MC	Cingulate Gyrus - WM	L	24	-9	-5	33	2.04/	8
			31	-16	-50	32	2.33/	10
		R	24	6	23	17	3.01/	6
			31	13	-34	27	3.24/	37
	Parietal Lobe – WM	L		-27	-34	29	2.51/	6
	Precuneus – WM	R	31	21	-50	32	2.4/	7
LPC	Supramarginal Gyrus*	L	39	-46	-57	31	2.04/	6
Subcortical								
MTL	Hippocampus	R		36	-31	-5	2.89/	9
Striatum	Putamen	L		-19	18	-2	4.21/	26
	Claustrum	R		36	-13	7	4.08/	9
[HC Targets + Target Accuracy] inclusively masked with [HC Targets – Target RT]								
Cortical							+Acc/-RT	
LPC	Superior Parietal Lobe*	R	7	35	-69	42	3.14/1.89	6
Regions associated with decreased attentional control and impaired task performance								
[HC Targets - API] inclusively masked with [HC Targets + Target RT]								
Cortical							-API/+RT	
dlPFC	Superior Frontal Gyrus*	L	10	-31	53	20	3.07/2	6
	Middle Frontal Gyrus - WM	R		24	-5	37	2.55/2.08	5
Insula	Insula	L		-31	-7	18	3.32/2.5	6
		R		36	-11	22	3.22/3.66	13
MC	Dorsal Anterior Cingulate*	R	32	10	10	34	3.61/1.8	9
LPC	Inferior Parietal Lobe*	L	40	-42	-50	35	2.88/2.39	9
TOC	Superior Temporal Lobe	R	22	43	-25	6	2.6/1.99	6
Subcortical								
Striatum	Caudate	R		21	25	3	2.85/1.86	6
	Claustrum	R		28	8	20	3/2.63	12

Thalamus	Pulvinar	R		10	-33	16	3.28/2.67	8
[CA Targets - API] inclusively masked with [CA Targets + Target RT]								
Cortical								
dlPFC	Middle Frontal Gyrus*	L	6	-28	-3	58	3.48/2.7	13
		R	6	43	12	49	2.59/2.45	5
vlPFC	Inferior/Middle Frontal Gyrus*	R	47	40	37	-6	2.41/3.18	7
MC	Ventral Anterior Cingulate/Superior Frontal Gyrus*	R	32/10	14	43	5	2.77/1.92	21
	Posterior Mid-Cingulate	L	31	-5	-24	42	3.98/2.54	26
	Superior Frontal Gyrus*	L	8	-13	39	51	3.61/5.51	33
				-35	20	52	2.53/2.03	5
	Superior Frontal Gyrus*	R	6	9	23	61	3.07/2.28	34
	Ventral Medial Frontal Gyrus*	L	10	-8	54	13	2.29/2.81	9
	Medial Frontal Gyrus		6	-9	5	51	2.49/2.38	5
	Precuneus	R	7	9	-48	54	3.97/1.80	5
LPC	Postcentral Gyrus	L	5/3	-24	-41	61	3.86/2.61	155
			40	-53	-22	19	3.11/2.12	8
		R	2	58	-21	43	2.67/3.46	11
	Inferior Parietal Lobe*	L	40	-54	-43	43	3.22/2.63	5
TOC	Lingual Gyrus	L	18	-5	-62	2	5.35/2.42	242
		R	19	17	-57	-4	4.28/2.53	
	Cuneus	L	18	-20	-86	17	5.34/2.95	47
		R	18	13	-80	29	3.83/2.34	7
	Fusiform Gyrus	L	19	-38	-64	-10	3.32/1.81	15
		R	19	28	-79	-10	3.86/1.86	12
	Inferior Temporal Gyrus	L	37	-46	-69	1	2.81/1.88	13
		R	20	47	-7	-17	3.39/3.77	24
			19	51	-62	-1	2.56/2.02	5
	Superior Temporal Gyrus	R	22	51	6	-1	2.62/2.49	10
	Middle Occipital Gyrus	R	18	36	-84	1	3.97/2.22	13
Subcortical								
MTL	Amygdala	R		25	-4	-17	2.54/2.32	11
Striatum	Putamen	R		18	11	-12	2.75/2.52	12
	Caudate Body	L		-12	1	19	3.74/2.76	12
Thalamus	Pulvinar	L		-16	-32	8	3.42/2.14	12

The displayed t-values correspond to peak voxels from the individual correlation maps used to create the conjunction maps. Individual maps were created with a p-value of 0.05. Thus the conjunction map had a joint threshold of $p \leq 0.0025$. Asterisks indicate cluster(s) also served as seed region for functional connectivity analysis. BA, Brodmann area; L, left; R, right; HC, healthy control; CA, clinical adolescent; API, attention performance index; RT, reaction time; dlPFC, dorso-lateral prefrontal cortex; vlPFC, ventro-lateral prefrontal cortex; MC, medial cortex; FC, frontal cortex; LPC, lateral parietal cortex; TOC, temporal-occipital cortex; MTL, medial temporal lobe.

Table 6-4. Common brain regions showing greater functional connectivity for HCs (Top) and CAs (Bottom) between frontal and parietal ROIs identified when assessing group differences in mean activity in response to targets.

Brain Regions		Hemi.	BA	Talairach Coordinates x	y	z	T-Value (minimum T)	Cluster Size
Common brain regions of increased connectivity for HCs.								
[R. MFG, HC Targets > CA Targets] inclusively masked with [L. MFG, HC Targets > CA Targets] and [L. IPL, HC Targets > CA Targets] and [HC Targets > Distracters]								
Cortical							HC > CA	
dlPFC	Superior Frontal Gyrus	L	10/9	-23	54	13	2.17	22
		R	10/9	21	53	17	3.65	70
			8	32	20	50	2.86	24
	Middle Frontal Gyrus	R	6/8	32	12	56	2.09	
		L	9/8	-35	37	36	2.29	11
MC	Medial Frontal Gyrus WM	L		17	1	48	2.34	37
LPC	Postcentral Gyrus	L	2	-53	-24	44	4.35	410
	Inferior Parietal Lobe	L	40	-53	-35	43	3.89	
		R	40	46	-62	46	3.69	140
TOC	Middle Temporal Gyrus WM	R		51	-31	-9	2.5	20
Subcortical								
Striatum	Caudate Head	L		-16	17	2	2.38	9
	Caudate Body	R		14	20	10	2.29	7
Cerebellum								
Anterior Lobe	Dentate	R		14	-52	-22	2.61	23
[R. MFG, HC Targets > CA Targets] inclusively masked with [L. MFG, HC Targets > CA Targets] and [HC Targets > Distracters]								
Cortical								
dlPFC	Middle Frontal Gyrus	L	8/9	-27	28	43	2.72	24
	Superior Frontal Gyrus	L	9	-31	49	26	2.15	36
	Superior Frontal Gyrus	R	9/10	28	48	35	2.54	88
MC	Anterior Cingulate	R	32	18	43	5	2.47	
	Superior/Medial Frontal Gyrus	R	8/6	17	0	59	3.73	146
LPC	Inferior Parietal Lobe	L	40	-46	-33	51	4.47	1184
		R	40	43	-55	47	4.96	
	Postcentral Gyrus	L	2	-53	-24	44	4.35	
TOC	Middle Temporal Gyrus WM	R		51	-31	-9	2.5	20
Subcortical								
Striatum	Caudate Body/Head	L		-16	17	6	2.44	16
	Caudate Body	R		14	20	10	2.52	14
Cerebellum								
Anterior Lobe	Culmen/Dentate	R		21	-56	-22	2.8	29

[R. MFG, HC Targets > CA Targets] inclusively masked with [L. MFG, HC Targets > CA Targets] and [HC Distracters > Targets]								
vlPFC	Inferior Frontal Gyrus	R	45	40	20	10	2.29	17
TOC	Fusiform Gyrus	R	37	47	-61	-11	3.31	59
	Middle / Inferior Occipital Gyrus	L	19	-38	-76	-7	3.29	63
	Superior Temporal Gyrus	R	22	47	-56	14	3.26	42
	Lingual Gyrus	L	18	-16	-76	-7	2.16	17
Subcortical								
MTL	Parahippocampus	L	27	-16	-27	-6	2.07	5
		R	36	29	-22	-19	2.34	9
Cerebellum								
Anterior Lobe	Culmen	L		-31	-56	-20	2.33	18
Common brain regions of increased connectivity for CAs.								
[R. MFG, CA Targets > HC Targets] inclusively masked with [L. MFG, CA Targets > HC Targets] and [CA Targets > Distracters]								
Cortical							CA > HC	
MC	Corpus Callosum WM	R		10	-33	16	3.69	17
TOC	Temporal Lobe WM	R		28	-41	19	2.56	14
[R. MFG, CA Targets > HC Targets] inclusively masked with [L. MFG, CA Targets > HC Targets] and [CA Distracters > Targets]								
Cortical								
MC	Posterior Cingulate	L	31	-13	-53	28	2.06	10

The displayed t-values correspond to voxels from the contrast with the smallest t-value contributing to the peak voxels in the conjunction map. Individual maps were created with a p-value of 0.05. Thus, the quadruple conjunction map had a joint threshold of $p \leq 0.00000625$ and the triple conjunction maps had a joint threshold of $p \leq 0.000125$. BA, Brodmann area; L, left; R, right; HC, healthy control; CA, clinical adolescent; WM, white matter; dlPFC, dorso-lateral prefrontal cortex; vlPFC, ventro-lateral prefrontal cortex; MC, medial cortex; FC, frontal cortex; LPC, lateral parietal cortex; TOC, temporal-occipital cortex; MTL, medial temporal lobe.

Table 6-5. Common brain regions showing greater functional connectivity for HCs for frontal and parietal ROIs identified when assessing brain-behavior relationships related to increased attentional control and task performance (top) and decreased attentional control and task performance (bottom).

Brain Regions		Hemi.	BA	Talairach Coordinates x	y	z	T-Value (minimum T)	Cluster Size
Common brain regions of increased connectivity for HCs linked to increased attentional control and enhanced task performance.								
[R. SFG, HC Targets > CA Targets] inclusively masked with [R. vACC, HC Targets > CA Targets] and [R. SPL, HC Targets > CA Targets] and [HC Targets > Distracters]								
Cortical							HC > CA	
dlPFC	Middle Frontal Gyrus	L	10	-34	45	22	2.56	26
		R	10	40	45	20	2.09	11
MC	Mid Cingulate Gyrus	R	31	6	-23	31	2.45	15
IC	Posterior Insula	L	13	-35	-30	22	2.49	97
LPC	Inferior Parietal Lobe	R	40/39	39	-54	36	2.7	27
	Superior Parietal Lobe	L	7	-24	-59	56	2.14	11
	Postcentral Gyrus	R	2/3	50	-19	29	2.28	32
[R. SFG, HC Targets > CA Targets] inclusively masked with [R. SPL, HC Targets > CA Targets] and [R. vACC, HC Targets > CA Targets] and [HC Distracters > Targets]								
Cortical								
dlPFC	Middle Frontal Gyrus	L	46	-46	34	21	2.37	16
		R	46	40	22	25	2.09	11
Common brain regions of increased connectivity for HCs linked to decreased attentional control and impaired task performance.								
[L. SFG, HC Targets > CA Targets] inclusively masked with [R. dACC, HC Targets > CA Targets] and [L. IPL vACC, HC Targets > CA Targets] and [HC Targets > Distracters]								
Cortical							HC > CA	
MC	Precuneus	L	7	-9	-74	48	2.58	24
		R	7	13	-51	50	2.35	11
			7	2	-44	47	2.16	12
	Medial Frontal Gyrus	L	6	-9	-14	57	2.02	18
Subcortical								
Striatum	Caudate Body	R		18	21	7	1.93	5
Cerebellum								
Anterior Lobe	Dentate	R		14	-48	-25	2.27	15
[L. SFG, HC Targets > CA Targets] inclusively masked with [R. dACC, HC Targets > CA Targets] and [L. IPL vACC, HC Targets > CA Targets] and [HC Distracters > Targets]								
Cerebellum								
Anterior Lobe	Culmen	L		-31	-56	-20	2.72	28
		R		29	-52	-22	2.51	22

The displayed t-values correspond to the voxel from the contrast with the smallest t-value contributing to the peak voxel in the conjunction map. Individual maps were created with a p-value of 0.05. Thus the quadruple conjunction map had a joint threshold of $p \leq 0.00000625$. BA, Brodmann area; L, left; R, right; HC, healthy control; CA, clinical adolescent; dlPFC, dorso-lateral prefrontal cortex; IC, insula cortex; MC, medial cortex; LPC, lateral parietal cortex.

Table 6-6. Brain regions showing greater functional connectivity for CAs for a parietal ROI identified when assessing brain-behavior relationships related to increased attentional control and task performance (top) and common brain regions showing greater functional connectivity for CAs for frontal ROIs identified when assessing brain-behavior relationships related to decreased attentional control and task performance (bottom).

Brain Regions		Hemi.	BA	Talairach Coordinates x	y	z	T-Value (minimum T)	Cluster Size
Brain regions of increased connectivity for CAs linked to increased attentional control and enhanced task								
[L. SMG, CA Targets > HC Targets] inclusively masked with [CA Targets > Distracters]								
Cortical							CA > HC	
dlPFC	Middle Frontal Gyrus	L	9	-27	22	35	2.39	32
		R	9/8	28	17	39	2.98	24
MC	Cingulate Gyrus	R	32	17	10	38	2.7	
			WM	17	-9	36	2.12	20
	Corpus Callosum	R		14	-37	15	3.05	12
FC	Precentral Gyrus	L	WM	-31	-8	28	2.61	15
LPC	Postcentral Gyrus	L	WM	-38	-30	30	2.31	12
[L. SMG, CA Targets > HC Targets] inclusively masked with [CA Distracters > Targets]								
Cortical								
Temporal Lobe	Superior Temporal Gyrus	R	22	47	-1	-9	2.1	11
Subcortical								
MTL	Hippocampus	R		29	-27	-9	2.27	12
Common brain regions of increased connectivity for CAs linked to decreased attentional control and impaired task performance.								
[L. vmPFC, CA Targets > HC Targets] inclusively masked with [R.vACC, CA Targets > HC Targets] and [CA Targets > Distracters]								
Cortical							CA > HC	
Temporal Lobe	Middle Temporal Gyrus	L	WM	-40	-4	-16	2.35	12
[L. vmPFC, CA Targets > HC Targets] inclusively masked with [R.vACC, CA Targets > HC Targets] and [CA Distracters > Targets]								
Cortical								
Temporal Lobe	Middle/Superior Temporal Gyrus	R	21/22	51	-8	-6	2.43	28
	Middle/Inferior Temporal Gyrus	L	21	-49	-15	-16	2.26	26
LPC	Postcentral Gyrus	R	2	28	-35	70	2.73	12
Subcortical								
MTL	Amygdala	R		29	-4	-14	2.26	16
	Hippocampus	R		33	-15	-18	1.98	31
	Parahippocampus	R	35	21	-35	-6	3.07	
		L	36	-27	-34	-10	2.24	8

The displayed t-values correspond to the voxel from the contrast with the smallest t-value contributing to the peak voxel in the conjunction map. Individual maps were created with a p-value of 0.05. Thus, the double and triple conjunction maps had a joint threshold of $p \leq 0.0025$ and 0.000125, respectively. BA, Brodmann area; L,

left; R, right; HC, healthy control; CA, clinical adolescent; dlPFC, dorso-lateral prefrontal cortex; FC, frontal cortex; MC, medial cortex; LPC, lateral parietal cortex; MTL, medial temporal lobe.

Table 6-7. Brain regions showing greater functional connectivity for HCs for a parietal ROI identified when assessing brain-behavior relationships in CAs related to increased attentional control and task performance (top) and frontal ROIs identified when assessing brain-behavior relationships in CAs related to decreased attentional control and task performance (bottom).

Brain Regions		Hemi.	BA	Talairach Coordinates x	y	z	T-Value (minimum T)	Cluster Size
Brain regions of increased connectivity for HCs for the seed region in CAs related to increased attentional control and task performance.								
[L. SMG, HC Targets > CA Targets] inclusively masked with [HC Targets > Distracters]								
Cortical							HC > CA	
dlPFC	Superior Frontal Gyrus	L	8	-31	17	49	2.35	20
	Middle Frontal Gyrus	L	10	-34	51	8	1.76	24
		R	6	28	8	52	2.95	41
MC	Anterior Cingulate Gyrus	R	32	18	39	5	3.04	15
	Precuneus	L	7	-13	-74	48	2.69	24
		R		6	-48	54	2.23	16
LPC	Inferior Parietal Lobe	L	40	-46	-44	50	3.31	83
	Superior Parietal Lobe		7	-35	-59	52	2.54	
		R	7	35	-66	45	2.59	34
	Supramarginal Gyrus	L	40	-61	-49	24	2.73	16
IC	Posterior Insula/Transverse Temporal Gyrus	L	13/41	-38	-29	15	2.67	83
TOC	Middle Temporal gyrus	L	21	62	-31	-8	2.52	34
		R	21	-53	-4	-11	2.37	26
Subcortical								
Thalamus	Ventral Lateral Nucleus	L		-12	-11	17	2.26	6
	Ventral Posterior Lateral Nucleus			-16	-17	6	2.18	11
Cerebellum								
Anterior Lobe	Dentate	R		18	-56	-22	3.55	53
[L. SMG, HC Targets > CA Targets] inclusively masked with [HC Distracters > Targets]								
Cortical								
dlPFC	Precentral Gyrus	R	4	39	-18	57	2.22	13
	Middle Frontal Gyrus	L	46	-46	27	20	2.64	93
vlPFC	Inferior Frontal Gyrus	L	45	-45	20	9	2.54	
			45	-45	40	4	2.58	11
			47	-27	12	-20	2.85	23
MC	Anterior Cingulate	L	32	-5	44	1	2.99	64
		R	24	3	36	4	2.55	
	Precuneus	L	23	-1	-63	20	2.31	11
	Superior Frontal Gyrus	L	6	-9	31	54	2.71	67
Temporal Lobe	Superior Temporal Gyrus	R	38	40	17	-33	2.21	18
TOC	Middle Temporal Gyrus	R	39	43	-68	24	2.8	25

	Fusiform Gyrus	R	37	47	-60	-15	2.43	13
	Middle/Inferior Occipital Gyrus	R	18	28	-84	-3	2.64	62
Subcortical								
MTL	Uncus	L		-23	8	-21	2.77	8
Cerebellum								
Anterior Lobe	Culmen	L		-34	-56	-20	2.81	86
		R		29	-56	-19	3.9	93
Common brain regions of increased connectivity for HCs for the seed regions in CAs related to decreased attentional control and task performance.								
[L. vmPFC, HC Targets > CA Targets] inclusively masked with [R. vACC, HC Targets > CA Targets] and [HC Targets > Distracters]								
Cortical							HC > CA	
MC	Medial Frontal Gyrus	R	WM	13	-15	61	2.28	11
	Precentral Gyrus/Medial Frontal Gyrus	L	4/6	-13	-26	59	3.58	84
	Precuneus	R	7	13	-63	49	2.51	21
LPC	Inferior Parietal Lobe	L	40	-46	-30	26	3.62	866
	Inferior Parietal Lobe/Precuneus	R	WM	28	-40	44	3.47	731
Subcortical								
Striatum	Caudate	R		17	4	23	2	10
Thalamus	Ventral Lateral Nucleus	L		-16	-14	14	2.31	18
[L. vmPFC, HC Targets > CA Targets] inclusively masked with [R.vACC, HC Targets > CA Targets] and [HC Distracters > Targets]								
Cortical								
dlPFC	Inferior Frontal Gyrus	L	9/44	-42	12	23	3.22	77
	Middle Frontal Gyrus		9	-42	10	37	2.32	
		R	9	39	22	29	3.18	80
			6	43	2	38	2.32	

The displayed t-values correspond to the voxel from the contrast with the smallest t-value contributing to the peak voxel in the conjunction map. Individual maps were created with a p-value of 0.05. Thus, the double and triple conjunction maps had a joint threshold of $p \leq 0.0025$ and 0.000125, respectively. BA, Brodmann area; L, left; R, right; HC, healthy control; CA, clinical adolescent; dlPFC, dorso-lateral prefrontal cortex; vlPFC, ventro-lateral prefrontal cortex; IC, insula cortex; MC, medial cortex; LPC, lateral parietal cortex; TOC, temporal occipital cortex; MTL, medial temporal lobe.

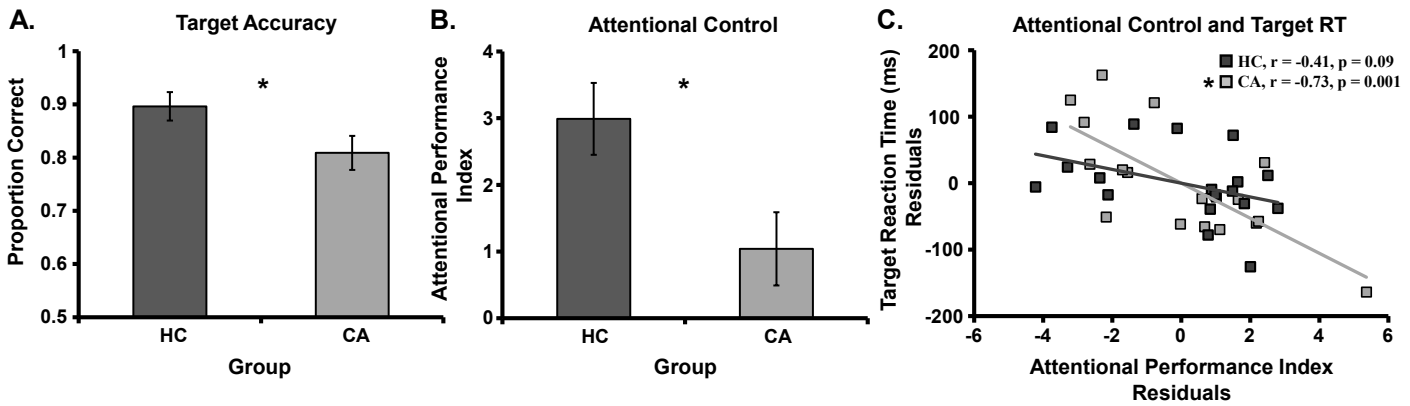

Figure 6-1. Task and attentional control deficits in clinical adolescents. Panel A shows a significant decrease for CAs compared to HCs in averaged accuracy data for targets (collapsed across target types). Panel B shows significantly reduced attentional control for CAs as determined from averaged attentional performance index scores for each group. Panel C shows the relationship between task performance and attentional control for clinical and healthy control adolescents separately. For both groups, target RT decreased as attentional control scores increased, but this relationship was only significant for CAs.

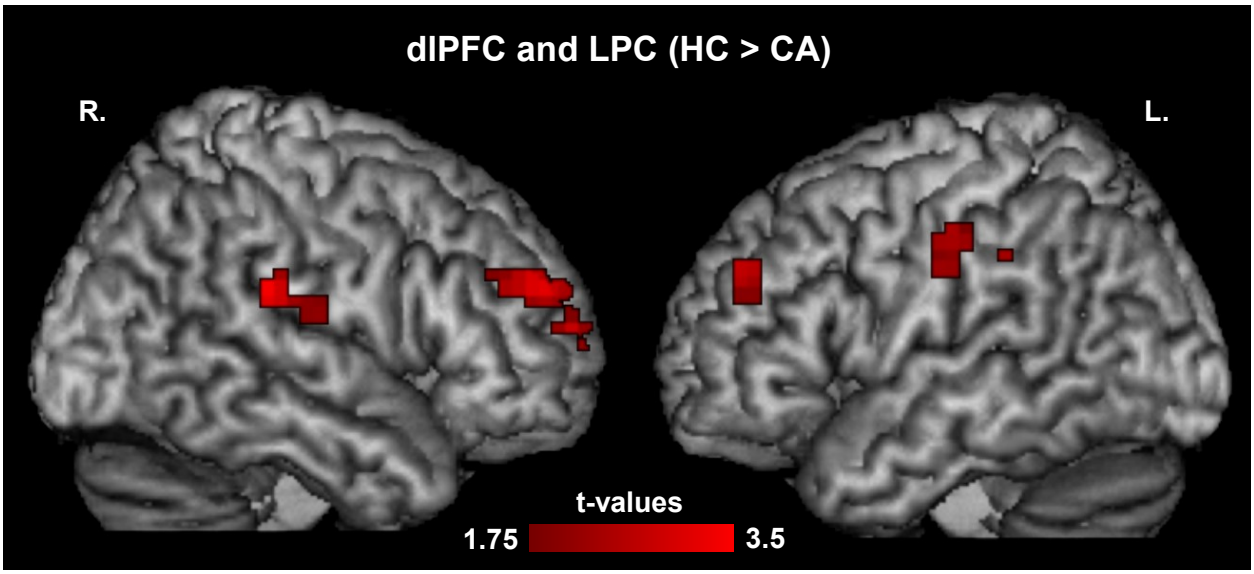

Figure 6-2. Brain regions showing reduced activation to Targets for Clinical Adolescents. Image shows dlPFC and LPC regions with significantly reduced response to targets for clinical compared to healthy control adolescents. The final activation map is superimposed on a high resolution brain image displayed in tridimensional view using MRIcron. The displayed activation map is a triple conjunction map. The individual maps comprising the triple conjunction map assessed 1) group differences in target processing (HCs > CAs), 2) target activity greater than baseline for HCs, and 3) and target greater than distracter activity for HCs. The independent probabilities were $p \leq 0.05$, $p \leq 0.005$, and $p \leq 0.005$, respectively. HC, healthy controls; CA, clinical adolescents; L., left; R., right; dlPFC, dorso-lateral prefrontal cortex; LPC, lateral parietal cortex.

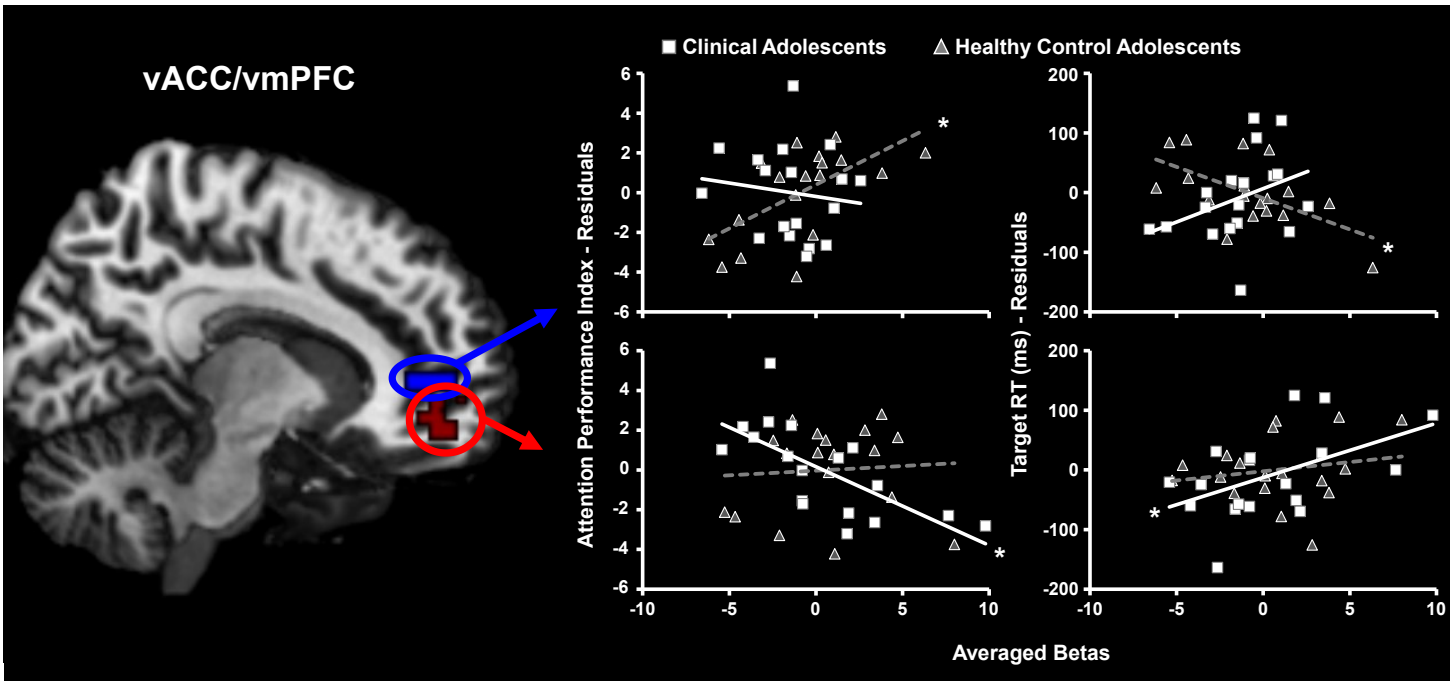

Figure 6-3. Group dissociation in the relationship between vACC engagement during target processing and individual differences in attentional control and task performance. Image shows vACC activity positively correlated with individual differences in attentional control and negatively correlated with target reaction time (RT) for HCs – blue blob. Image also shows vACC activity negatively correlated with individual differences in attentional control and positively correlated with target RT – red blob. The scattergrams show the relationship between attentional control scores (left column), target RT (right column) and averaged beta-values extracted for each cluster. Asterisks indicate the relationship corresponding to the adjacent trendline was significant ($p \leq 0.05$). The final activation maps are superimposed on a high resolution brain image displayed in tridimensional view using MRIcron. The displayed activation maps are double conjunction maps. The individual maps comprising the final conjunction maps assessed a positive/negative covariation with attentional control and negative/postivie covariation with target RT, respectively. The independent probabilities were $p \leq 0.05$ and $p \leq 0.05$. HC, healthy controls; CA, clinical adolescents; vACC, ventral anterior cingulate cortex; vmPFC, ventral medial prefrontal cortex.

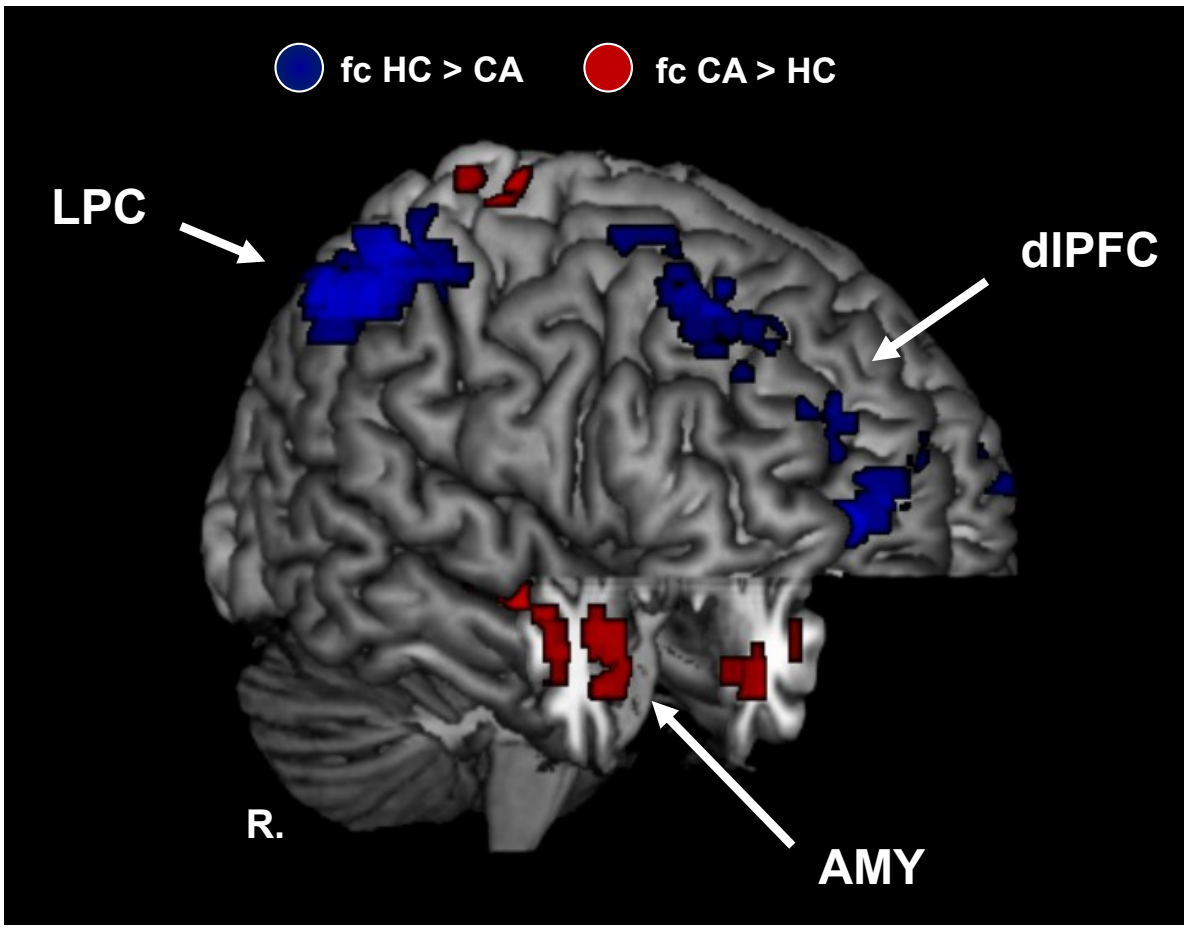

Figure 6-4. Brain regions comprising different functional networks engaged during target processing for clinical and healthy control adolescents. Image shows brain regions with increased functional connectivity (fc) for HCs compared to CAs during target processing in dorsal frontal and parietal cognitive control regions (blue blobs). Image also shows brain regions with increased fc for CAs compared to HCs during target processing in ventral emotion processing regions (red blobs). The final activation maps are superimposed on a high resolution brain image displayed in tridimensional view using MRIcron. The displayed activation maps are conjunction maps. The final conjunction map for HC > CA (blue blobs) was comprised of four separate maps; three assessed fc for seed regions identified by group differences in mean target activity (i.e., R.MFG, L.MFG, L.IPL) and the fourth restricted activation to areas involved in target processing (i.e., target > distracter activity for HCs). The final conjunction map for CA > HC (red blobs) was comprised of three separate maps; two assessed fc for seed regions identified when examining brain-behavior relationships related to impaired performance and attentional control (i.e., left and right vACC/vmPFC) and the third examined whether these areas were also associated with general distracter processing (i.e., distracter > target activity for CAs).
The independent probability for all maps was $p \leq 0.05$. HC, healthy controls; CA, clinical adolescents; R., right; vACC, ventral anterior cingulate cortex; vmPFC, ventral medial prefrontal cortex; MFG, middle frontal gyrus; IPL, inferior parietal lobe; dlPFC, dorso-lateral prefrontal cortex; LPC, lateral parietal cortex; AMY, amygdala.

CHAPTER 7

ALTERATIONS IN WHITE MATTER MICROSTRUCTURE ASSOCIATED WITH ADOLESCENT PSYCHOPATHOLOGY – DTI EVIDENCE

A Diffusion Tensor Imaging Investigation of White Matter Microstructural Changes Linked to Adolescent Psychopathology

A version of this chapter is currently being prepared for peer-reviewed publication

Adolescence is a transitional development period from childhood to young adulthood and is characterized by structural and functional brain maturation, pubertal changes, and social, cognitive, and emotional development (Spear, 2000). This developmental period is especially unique as behaviorally, it is associated with increases in risk-taking, but also by increases in cognitive control and regulatory processes (Luna, Garver, Urban, Lazar, & Sweeney, 2004; Luna & Sweeney, 2004; Rosso, Young, Femia, & Yurgelun-Todd, 2004; Steinberg, 2004). Healthy adolescents engage in risk taking behaviors and often experience behavioral problems (Maggs, Almeida, & Galambos, 1995). Risky behaviors have been shown to be exacerbated in adolescents with psychopathology (Kaess et al., 2014; Zhou et al., 2012). In accompaniment with increased risk taking is increased mortality, and accidents are the leading cause of death among adolescents (ages 15 – 19) as reported by the Centers for Disease Control and Prevention (CDC and Prevention, 2014). Along with the increased mortality due to risky behaviors, suicide is the third leading cause of death among adolescents (Heron, 2013). Furthermore, psychiatric disorders are a leading risk factor for suicide (Moscicki, 2001). Therefore, understanding adolescent psychopathology is of paramount importance as these individuals are at increased risk for adolescent mortality.

While many aspects of adolescent psychopathology are debated, there is some consensus that encountering an abnormal amount difficulties (regardless of why – i.e., genetic, psychobiological, environmental, or a combination thereof) in navigating developmental challenges confronted during this transitional period may be representative of underlying psychopathology (Price & Zwolinski, 2010). Identifying differences in neural structure and function that are potentially associated with adolescent psychopathology is important for creating biomarkers of mental health dysfunction and informing therapeutic interventions. One method

for identifying structural differences associated with psychopathology is diffusion tensor imaging (DTI). DTI offers a non-invasive technique to examine white matter microstructure [i.e., orientation, composition, and integrity, but see Jones and colleagues (2013) for the importance of appropriate context when making claims about integrity] and has provided empirical support for aberrant connectivity in adult psychiatric disorders (e.g., Abe et al., 2006; Adler et al., 2004; Alexopoulos, Kiosses, Choi, Murphy, & Lim, 2002; Bae et al., 2006; Beyer et al., 2005; Cannistraro et al., 2007; Kim et al., 2006; Rusch, Luders, et al., 2007; Rusch, Weber, et al., 2007; Szeszko et al., 2005; Taylor, MacFall, Gerig, & Krishnan, 2007). Moreover, faulty white matter microstructure has been shown to contribute to the pathophysiology of the disorder (Fields, 2008; White & Lim, 2011). However, alterations in white matter microstructure in adolescents with psychiatric disorders remain less clear. The overarching goal of the current investigation is to identify white matter changes differentiating typical from atypical (psychopathological) adolescent behavior and development.

The implementation of DTI to investigate white matter properties relies on the principle that water diffusion in healthy white matter is anisotropic (see Beaulieu, 2013 for review). One methods of quantifying water diffusion is calculating fractional anisotropy (FA, Basser & Pierpaoli, 1996). This offers a simple way of comparing the overall anisotropy of an area of tissue as FA values range from 0-isotropic to 1-anisotropic. Second, although FA offers a good index of overall anisotropy it is sensitive to many tissue characteristics that result in changes in anisotropy [e.g., the degree of myelination, fiber coherence, fiber density, axon diameter, tract geometry, presence of crossing fibers, (Beaulieu, 2002, 2013)]. Therefore, interpreting FA in the context of other diffusivity parameters can allow for more informed inferences to be made about the characteristics of the tissue microstructure (Alexander, Lee, Lazar, & Field, 2007; Oh, Henry,

Genain, Nelson, & Pelletier, 2004; Pierpaoli et al., 2001; Song et al., 2003; Song et al., 2002). Three additional diffusivity parameters are typically employed to do this. The first, axial diffusivity (AD) represents the direction where diffusion is the greatest within a voxel (i.e., parallel with the direction of white matter fiber tracts). The second, radial diffusivity (RD) represent diffusion perpendicular to the main white matter axis in the voxel. The third, mean diffusivity (MD) represents general diffusivity within a voxel regardless of directionality.

Previous research examining white matter changes in adolescence has shown continued development of white matter (as indexed by increased FA and decreased MD) throughout adolescence into adulthood, with some tracts reaching their maximum FA during teen years and other not until mid-twenties (Barnea-Goraly et al., 2005; Bava et al., 2010; Ben Bashat et al., 2005; Bonekamp et al., 2007; Giorgio et al., 2008; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008; Mukherjee et al., 2001; Schmithorst, Wilke, Dardzinski, & Holland, 2002). During adolescence increased FA and decreased MD have been found to be largely driven by decreases in RD (Qiu, Tan, Zhou, & Khong, 2008). Enhanced FA and reduced RD during development is thought to reflect increases in myelination (Beaulieu, 2002; Song et al., 2002). Increases in FA and in AD during development have been suggested to describe fiber coherence (Dubois et al., 2008). These studies have provided information on typical white matter development during adolescence and the information gleaned is necessary in identifying and understanding when things go wrong during development as may be the case with adolescent psychopathology.

Although a number of studies in the last decade have begun to shed light on white matter changes during adolescence, alterations in white matter during adolescence due to psychopathology remain largely unknown. Extant research on adult psychopathology show large

spatial heterogeneity in the location of white matter abnormalities found in various psychiatric disorders (see Fields, 2008 for review). However, due to the high degree of co-morbidity in adolescent psychopathology (Knapp & Jensen, 2006), adolescent psychopathology may be best described as a constellation of co-occurring disorders (Price & Zwolinski, 2010). As a result, there may be overarching similarities in areas impacted in adolescent psychopathology that are not specific to one disorder (Sauder, Beauchaine, Gatzke-Kopp, Shannon, & Aylward, 2012; Singhal et al., 2012). The extant research on microstructural white matter changes in clinical adolescents is limited and the findings are somewhat conflicting, but the majority of studies show decreases in FA compared to non-clinical, control adolescents (Ashtari et al., 2005; Cullen et al., 2010; Frazier et al., 2007; Haney-Caron, Caprihan, & Stevens, 2014; Henderson et al., 2013; Jacobson et al., 2010; Li, Mathews, Wang, Dunn, & Kronenberger, 2005; Lin et al., 2012; Pavuluri et al., 2009; Wang et al., 2012). Although a few studies have found increases in FA in certain white matter tracts for specific subsets of clinical adolescents [see (Silk, Vance, Rinehart, Bradshaw, & Cunnington, 2009) for increases in FA with attention deficit hyperactive disorder, ADHD ; (Cardenas et al., 2013) for increases in FA with alcohol use disorders; and (Sarkar et al., 2013) and (Passamonti et al., 2012) for increases in FA with conduct disorder, CD]. Therefore, alternations in white matter microstructure in adolescence due to psychopathology remain unclear. Differences in methodology [voxel (e.g., tract-based spatial statistics, TBSS) vs. ROI-based (e.g., tractography)], sample heterogeneity, and individual differences in the development of executive function (Lebel et al., 2013; Seghete, Herting, & Nagel, 2013; Treit, Chen, Rasmussen, & Beaulieu, 2014) may account for these discrepancies across studies.

The current study investigated three main issues with respect to potential changes in white matter microstructure associated with clinical psychopathology. First, we examined

general overall differences in FA values between a group of clinical adolescents with affective, attention, and behavioral axis-I mental health disorders and their healthy control counterparts. Second, we investigated the pattern of diffusivity parameters in areas showing overall differences in FA. Third, we assessed similarities and differences in white matter development between these two groups. We made the following three predictions based on extant literature. First, we predicted that adolescents with psychopathology would show overall decreased white matter integrity as indicated by smaller FA values compared to adolescents without psychopathology. Second, we predicted that the pattern of diffusion parameters in clinical adolescents would be consistent with the delayed development of white matter (e.g., reduced membrane density, axon fragmentation, and decreased myelination). Finally, we predicted that while overarching similarities would exist in white matter development across clinical and healthy adolescents, more differences in the relationship between age and white matter development between groups would be identified, specifically in association fibers.

Methods

Participants. Forty [20 clinical (8 male, 1 left-handed), 20 non-clinical (8 male, 1 left-handed)] adolescents (12 – 17 years; Mean = 15) participated in the study. The clinical adolescents (CLAs) were recruited from a residential mental-health treatment facility in the City of Edmonton, Alberta, Canada. These adolescents were clinically diagnosed with diagnostic and statistical manual of mental health disorders 4th edition (DSM-IV) Axis-1 disorders. Due to the large comorbidity and heterogeneity in our sample's diagnoses we grouped depressive disorders (major depression and dysthymia) and anxiety disorders (generalized anxiety, post-traumatic stress disorder, social phobia) together into one 'distress disorders' category. We also grouped all sub-types of ADHD (combined, predominantly inattentive type, predominantly

hyperactive/impulsivity type) together into one 'ADHD' category. Clinical characteristics are summarized in Table 1. Non-clinical, healthy control adolescents (HCAs) recruited from the City of Edmonton, were screened for psychiatric illness and drug/alcohol use with the mini-international neuropsychiatric interview for kids [M.I.N.I-Kid, (Sheehan et al., 1998; Sheehan et al., 2010)]. Healthy controls were matched to CLAs on age (within 1 year from time of scanning), sex, and handedness. All participants had normal or corrected-to-normal vision. Informed consent and assent were obtained from parental guardians and adolescents before participating. The experimental protocol was approved for the ethical treatment of human participants by the Health Research Ethics Board at the University of Alberta.

[Insert Table 1 about here]

Data Acquisition. DTI data were acquired on a 1.5T Siemens Sonata MRI scanner using a dual spin-echo, single shot echoplanar imaging sequence with the following parameters: 50, 2.2-mm thick slices with no inter-slice gap and an in-plane resolution of 2.2 mm x 2.2 mm, TR = 7700 ms, TE = 94 ms, 30 diffusion sensitizing gradient directions with b = 1000 s/mm^2, 5 non-diffusion-weighted, T2 images (b = 0 s/mm^2), field of view 212 x 212 mm^2. Total DTI acquisition time was 4:39 min.

DTI Image Processing. DTI data were processed using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB, FSL5.0.6) Diffusion Toolbox (FDT). First, raw data were screened for artifacts and slices with artifacts/signal dropout were removed. No more than 5 diffusion weighted slices were removed for a signal subject. Second, all non-diffusion weighted (b0) images were motion and eddy current corrected using FMRIB's linear registration tool (FLIRT, Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001), and then averaged. This corrected non-diffusion average was then used as the template for

motion and eddy current correction of the non-diffusion weighted and diffusion weighted images separately. These corrected non-diffusion and diffusion weighted images were then combined for use of the brain extraction tool (BET; Smith, 2002), creating a mask to be used for tensor fitting. The fractional intensity threshold was set at 0.3 as this was found to provide the best results across subjects. The diffusion tensor model was fit at each voxel using DTIFIT with weighted least-squares regression (Abdi, 2003; Jones, Knosche, & Turner, 2013).

Whole Brain FA Analysis. FMRIB's tract-based spatial statistics (TBSS) toolbox was used to prepare the FA images for statistical analysis. Every individual FA image was aligned to every other FA image to identify the most representative image (the image that requires the least amount of warping) using the nonlinear registration tool FNIRT (Andersson, Jenkinson, & Smith, 2007a, 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The most representative FA image was then affine-aligned to 1 mm^3 MNI152 standard space. All other individual FA images were transformed into 1 mm^3 MNI152 standard space by combining the affine transform of the most representative FA image to MNI152 space with the non-linear (FNIRT) transform to the most representative FA image. These transformations were combined before being applied (see appendix A for a representative FA map). Aligning individual FA images to the most representative FA image within our sample rather than to an FA template was done as a result of working with adolescents, where the adult-derived FA template is inappropriate. All 40 individual standardized FA images were merged into a single 4D image for statistical analysis. A sample specific mask was then created to eliminate cross-subject variability and ensure only FA values associated white matter were included in the analysis, thus eliminating those associated with grey matter and cerebral spinal fluid. To create the sample specific mask a FA threshold of 0.2 was applied to each individual

standardized FA image and then binarized such that voxels with a FA value greater than 0.2 were assigned a value of 1 and those not meeting the FA threshold were given a value of 0. All binary images were then multiplied to create the mask image, thus any voxel not meeting the FA threshold across participants was dropped from analysis.

To examine group differences standardized FA images were entered into a non-parametric, voxel-wise, two-sample permutation test using FMRIB's Randomise with 5000 permutations and variance smoothing kernel of 2 mm^3 (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Analysis was restricted to voxels included in the sample specific white matter mask. Although subjects were age-matched within one year of age at the time of scanning, adolescence is a time of large white matter maturation (Lebel et al., 2008) and one-year may be too large of difference to adequately control for these effects. Therefore, any potential effects due to age were removed by entering age as demeaned covariate. Correction for multiple comparison was performed using Monte Carlo simulation implemented in AFNI [AlphaSim, http://afni.nimh.nih.gov, (Forman et al., 1995; Xiong, Gao, Lancaster, & Fox, 1995)] on the sample specific white matter mask and incorporated the size the variance smoothing kernel implemented in Ransomise (2 mm^3). Clusters larger than 29 mm^3 at a threshold of $p \leq 0.005$ (corresponding to a FWE $\alpha = 0.05$) were considered significant. The JHU-ICBM-DTI-81 White-Matter Labels Atlas and MRI atlas of human white matter were used to identify the anatomical location of significant clusters (Mori et al., 2008; Oishi, Faria, Van Zijl, & Mori, 2011; Oishi et al., 2008).

Diffusion Parameters Pattern Analysis Non-FA images were directly created from the DTIFIT output (i.e., AD, MD) or were calculated using the output images, [$RD = (\lambda_2 + \lambda_3)/2$]. Preparation for analysis was as follows: the non-linear and linear transformations from the FA image

standardization were applied to the AD, MD, and RD images resulting in all images being standardized in MNI152 1mm^3 space (see Appendix A for representative examples of each map). To examine group differences for these diffusion parameters, the standardized images were then subjected to the same statistical analysis and individual thresholding as reported above for the FA images. To examine potential changes in non-FA diffusion parameters in structures where significant differences in FA were identified we created conjunction images between each non-FA parameter and the FA image, [i.e., (FA ∩ AD), (FA ∩ MD), and (FA ∩ RD)]. Correction for multiple comparison on double conjunction images was performed using Monte Carlo simulation implemented in AFNI on the sample specific white matter mask, incorporated the size of the variance smoothing kernel, and used the product of the two independent p-values as the p-value threshold for the double conjunction image [e.g., 0.005 x 0.005 = 0.000025, (Fisher, 1950)]. Clusters larger than 10 mm^3 at a threshold of $p \leq 0.000025$ (corresponding to a FWE $\alpha < 0.05$) were considered significant. If two double conjunction images yielded significant clusters then a triple conjunction was performed between those non-FA diffusion parameters and FA. Correction for multiple comparison for a triple conjunction image was performed using Monte Carlo simulation implemented in AFNI on the sample specific white matter mask and used the product of the three independent p-values from the contributing images as the p-value threshold for the triple conjunction image. Clusters larger than 10 mm^3 at a threshold of $p \leq 0.000000125$ (corresponding to a FWE $\alpha < 0.05$) were considered significant.

Similarities and Differences in Age-Related FA Changes between Clinical and Healthy Adolescents To investigate similarities and differences in the relationship between age and FA for clinical and healthy adolescents, two sets of voxel-wise correlations were performed on the standardized FA images. One set (positive and negative correlations) was performed between

age and FA using only data for the healthy control adolescents. And the other set was performed between age and FA on the clinical adolescent's data. All correlations were performed by implementing non-parametric permutation tests with age as a regressor using Randomise with 5000 permutations, and a variance smoothing kernel of 2 mm^3. Analyses were restricted to voxels included in the sample specific white matter mask. Similarities between age and FA across groups were identified by creating two conjunction maps. One assessed similarities for the positive relationship between age and FA and the other similarities for the negative relationship between age and FA. For the conjunction analyses, the statistical threshold was determined as the product of the two independent p-values from the maps from which the conjunction was created (i.e., 0.05 x 0.05 = 0.0025). Correction for multiple comparison was performed using Monte Carlo simulation implemented in AFNI on the sample specific white matter mask and incorporated the size of the variance smoothing kernel. Clusters larger than 21 mm^3 at a threshold of $p \leq 0.0025$ (corresponding to a FWE $\alpha = 0.05$) were considered significant. Differences in the relationship between age and FA were examined by exclusively masking the each individual group correlation map with the corresponding conjunction map that was used to identify similarities between groups. For the exclusively masked correlation maps correction for multiple comparison was performed using Monte Carlo simulation implemented in AFNI on the sample specific white matter mask and incorporated the size of the variance smoothing kernel. Clusters larger than 153 mm^3 at a threshold of $p \leq 0.05$ (corresponding to a FWE $\alpha = 0.05$) were considered significant.

For significant clusters average FA values were then extracted for each participant and SPSS (SPSS Inc. Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.) was used to calculate Pearson r values. Where appropriate, differences between groups in

Pearson r coefficients were assessed by conversion to Fisher's Z (Fisher, 1921) followed by the calculation of a z-test statistic.

Results

Overall FA Decreases in Clinical Adolescents. To examine group differences in FA values a two-sample non-parametric permutation test with age as a covariate was performed. Twenty-six clusters were identified where FA values for CLAs were significantly less than FA values for HCAs. These 26 clusters covered 13 different white matter structures. Three of the white matter structures were lobar white matter [L. superior fontral gyrus (SFG-WM), R. cingulate gyrus (CG-WM), and L. superior temporal gyrus (STG-WM)]. Inter-hemispheric connections were also affected as the genu, body, and splenium of the corpus callosum all showed deficits in FA. Furthermore, subcortical-cortical connections were impacted with areas rich in projection fibers showing deficits in FA. These included the right superior corona radiata (SCR) and bilateral anterior corona radiata (ACR), bilateral anterior and posterior limb of the internal capsule (ALIC and PLIC, respectively), bilateral cerebral peduncle, and right posterior thalamic radiation (PTR). One association white matter structure showed differences between groups (R. uncinate fasciculus, UF). There were no FA increases for CLAs compared to HCAs.

Diffusivity Patterns in regions showing lowered FA in Clinical Adolescents. To determine the pattern of diffusivity parameters within the white matter structures showing group differences in FA, group differences in non-FA diffusion parameters were explored with a two-sample non-parametric permutation test with age as a covariate for AD, MD, and RD. A conjunction analysis was then performed between each non-FA diffusion parameter and FA. Five different patterns of diffusivity were identified in areas where CLAs had significantly smaller FA values compared to HCAs. First, differences in FA were found in the absence of change for any of the other

diffusion parameters in lobar white matter areas (right CG-WM, left STG-WM), in inter-hemispheric connections (bilateral portions of the genu and right splenium of the corpus callosum), and in subcortical-cortical connections (located in the right SCR, and in projections fibers in the left ALIC, and right PTR). Second, decreased FA for CLAs compared to HCAs was accompanied by decreased AD in inter-hemispheric connections (portions of the left genu and right body of the corpus callosum), and in subcortical-cortical connections, with both projection (right ACR, and left PLIC) and association [right UF (see Figure 1-A)] fibers identified. Third, decreased FA and increased RD was identified in lobar white matter (left SFG-WM, see Figure 1-B), in inter-hemispheric connections [portions of the genu (midline), and right body and splenium of the corpus callosum], and in subcortical-cortical projection fibers (left ALIC and PLIC, right cerebral peduncle). The fourth pattern of diffusivity consisted of decreased FA, decreased AD, in conjunction with increased RD. This pattern was identified in inter-hemispheric connections (right body of the corpus callosum), and in subcortical-cortical connections [left ACR (see Figure 1-C), and right PLIC (extending into the ALIC)]. The fifth pattern of diffusivity, identified only inter-hemispheric connections [left body of the corpus callosum (see Figure 1-D)], was decreased FA accompanied by increased RD and MD.

[Insert Figure 1 about here]

Similarities and Differences in Age-Related FA Changes between Clinical and Healthy Adolescents. To investigate similarities in the relationship between age and FA for healthy and clinical adolescents we performed two conjunction analyses (one for positive and one for negative correlations maps that were created for HCA and CLA groups separately). Two areas with subcortical-cortical projection fiber connections were found to be common to both clinical and healthy adolescents for a positive relationship between age and FA; the left SCR and right

posterior corona radiata (PCR, see Table 3). Whereas only one area, with subcortical connections, the left ansa lenticularis, was common across groups for a negative relationship between age and FA (see Table 3).

To examine differences in the relationship between age and FA for healthy and clinical adolescents we exclusively masked the individual group correlation maps with the conjunction maps created to assess similarities between the groups. Differences between groups were identified for both positive and negative correlations between age and FA (see Table 4). For healthy controls, eight clusters (with the peaks located in seven different white matter structures) were identified showing a positive relationship between age and FA. These structures included lobar white matter [left SFG –WM, left pre-central gyrus white matter (PrCG-WM), and right CG-WM], inter-hemispheric connections (left splenium), and subcortical-cortical connections (right ACR, bilateral SCR, and right PTR). For clinical adolescents, 20 clusters (the peaks of which were located in 11 white matter structures) showed a positive correlation between age and FA. The 11 structures where cluster peaks were identified consisted of lobar white matter (right SFG-WM, right superior occipital gyrus white matter (SOG-WM), inter-hemispheric connections (right genu, bilateral body of the corpus callosum), subcortical-cortical connections (bilateral ACR, SCR, PLIC, and right anterior/posterior ventrolateral thalamus white matter), and cortical-cortical connections [bilateral inferior fronto-occipital fasciculus (IFOF), bilateral superior longitudinal fasciculus (SLF), and bilateral sagittal stratum (see Table 4). Nine clusters (peaks located in seven white matter structures) were identified showing negative correlations between age and FA for HCAs. The seven structures consisted of lobar white matter (right SFG-WM), inter-hemispheric connections (right genu), subcortical-cortical connections (right PLIC, right PTR), and cortical-cortical connections (right external capsule, bilateral UF and right SLF).

For CLAs, a negative correlation between age and FA was identified in six clusters (peaks located in six white matter structures). These six structures consisted of lobar white matter [right SFG-WM, right STG-WM, middle temporal gyrus white matter (MTG-WM)], and areas with subcortical-cortical projection fibers (left ACR, right PLIC, and left PTR). A clear dissociation in the relationship between age and FA between groups was found in the genu of the corpus callosum (see Figure 2) where the same location showed a positive correlation for CLAs ($r = 0.62$, $p = 0.003$) and a negative correlation for HCAs ($r = -0.58$, $p = 0.007$). A second, although weaker, dissociation was identified in STG-WM (HCAs , $r = 0.39$, $p = 0.09$; CLAs, $r = -0.58$, $p = 0.007$).

[Insert Figure 2 about here]

Discussion

The current study investigated general and age-related differences in white matter microstructure between adolescents with and without Axis-I affective, attentional and behavioral disorders. This investigation yielded three main findings. First, decreases in overall white matter integrity (as indicated by smaller FA values) were identified for clinical compared to healthy control adolescents. These observed alterations in white matter integrity associated with adolescent psychopathology were found throughout a number of white matter structures sub-serving different functions in neural communication. These included lobar white matter, white matter involved in inter-hemispheric communication, and white matter important for cortical-cortical and subcortical-cortical connections. Second, further characterizing changes in overall white matter microstructure by examining specific patterns of diffusivity in non-FA diffusion parameters identified five patterns of diffusivity. Certain patterns, interpreted in the context of the developing brain, suggest differences in white matter microstructure between groups in some

areas may be largely due to delayed development (i.e., reduced myelination and/or decreased fiber coherence). Third, more differences than similarities were observed between groups in the relationship between FA and age. Commonalities were identified in two areas with subcortical-cortical connections and one area with subcortical-subcortical connections. Differences were identified in a number of white matter structures throughout the brain, with the clearest dissociation between groups for age-related FA changes found in the genu of the corpus callosum. Each of these main findings will be discussed below.

Overall FA Decreases in Clinical Adolescents with Affective, Attentional, and Behavioral Disorders

Our results showing a reduction of FA values for CLAs compared to HCAs is consistent with a number studies examining white matter microstructure in specific psychiatric disorders during adolescence. A unique aspect of the current investigation is that decreased FA was found regardless of the large heterogeneity of diagnosed axis-I disorders in our sample. Decreases in FA were found in frontal, midline, and temporal lobar white matter, throughout the corpus callosum (genu, body, and splenium), in a number of structures containing projection fibers (ACR, SCR, IC, CP, and PTR), and in one association fiber (UF). As a result of the comorbidity (especially heterotypic comorbidity, showing both externalizing and internalizing disorders), it is difficult to make direct comparisons to previous studies showing disorder specific alterations to one or more of the areas identified in the current investigation. However, the UF is consistently implicated in playing a part in neuropsychiatric disorders as this tract is involved in emotion processing connecting the anterior temporal lobe (amygdala and hippocampus) with the orbital cortex. Furthermore, it should be highlighted that white matter microstructural differences associated with the adolescent psychopathology present in our sample were identified in many

areas rich in projection fibers. Corticothalamic/thalamocoritcal fibers (i.e., thalamic radiations), corticofugal fibers (including corticopontine, corticoreticular, corticobulbar, and corticospinal tracts) have pathways through the internal capsule and fan out forming the corona radiata (Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). Interestingly, there may be link between decreases in white matter integrity in areas responsible for afferent and efferent processing of sensory and motor information, and impulsivity issues associated with developmental psychopathology (i.e., response inhibition). Impulse control (as measured through response inhibition paradigms) are tied to affective dysregulation and/or dysfunction of top-down control processes of goal-oriented action/behaviors (Luna & Sweeney, 2004; Somerville, Hare, & Casey, 2011). Decreased connectivity found in these areas also encourages contemplation of the link between embodied cognition and psychopathology (Fuchs & Schlimme, 2009).

In addition to the large number of areas with projection fibers that were impacted, the current findings show FA deficits throughout the corpus callosum linked to adolescent psychopathology. The corpus callosum is the main commissural fiber in the human brain and is thus responsible for the majority of inter-hemispheric communication. The anterior part of the corpus callosum (i.e., the genu) has connections with the prefrontal cortex (Hofer & Frahm, 2006). The midline section connects pre, supplementary and motor cortices (Hofer & Frahm, 2006). The posterior portion (i.e., the splenium) connects parietal, temporal and occipital areas (Hofer & Frahm, 2006; Putnam, Steven, Doron, Riggall, & Gazzaniga, 2010). The relationship between corpus callosum integrity and mental health has been established through research looking at agenesis of the corpus callosum (see Paul et al., 2007 for review) as well volumetric based and inter-hemispheric information transfer studies (Diwadkar & Keshavan, 2006; Gilliam

et al., 2011; Hiatt & Newman, 2007; Lopez et al., 2013). Decreases in FA for each major division of the corpus callosum (genu, body, and splenium) in CLAs support the notion that the inter-hemispheric communication necessary for higher order functioning (Gazzaniga, 2000) also plays an important and essential role in mental health.

Lobar or subgyral white matter differences in FA found in the SFG, CG, and STG suggest local, intracortical communication in these areas is impacted. As all three of these areas have known involvement in attentional processing [executive – SFG, (Hopfinger, Buonocore, & Mangun, 2000); reorienting – STG, (Corbetta, Patel, & Shulman, 2008)]; and emotion-cognition integration - CG, (Bush, Luu, & Posner, 2000)) their involvement in psychopathology is not surprising as research on functional alterations in psychopathology shows these areas to be impacted (Diwadkar & Keshavan, 2006; Luciana, 2006; Rothbart & Posner, 2006). It will be necessary for future research to examine the relationship between alterations in sub-gyral white matter and grey matter function (e.g., Ford & Kensinger, 2014, Daselaar S et al 2013) as it relates to psychopathology.

Diffusivity Patterns and Delayed Development in Regions Showing Lowered FA in Clinical Adolescents

Differences in FA may be driven by a predominating tissue characteristic, such as the amount of myelination, the degree of fiber coherence and density, the axon diameter, tract geometry, and the presence of crossing fibers. White matter microstructure is determined by some combination of these characteristics. In clinical populations differences in FA may be further informed by examining differences in other diffusion parameters. The current investigation identified five diffusivity patterns in structures where FA differences were found. These identified patterns, with the exception of pattern one, may offer more insight into which

tissue characteristics are driving changes in overall white matter integrity (as indexed by FA values). Pattern one, showing changes in FA in the absence of change in other diffusion parameters, reflects changes in tissue microstructure that are too subtle to be detected by significant differences in axial, radial, or mean diffusivities. Pattern two, decreased FA and AD in CLAs, suggest the changes in FA are driven by decreases in diffusion along the white matter tract. In the absence of changes in RD, this can be interpreted in the context of development as a potential decrease in white matter coherence as diffusivity only along the principal eigenvalue was impacted. Patterns three (decreased FA and increased RD in CLAs) and five (decreased FA and increased RD and MD in CLAs), may describe deficits in myelination (Song et al., 2002). Pattern four, decreased FA and AD along with increased RD, indicate longitudinal and transverse diffusion were both impacted and in the developing brain suggest decreased white matter coherence and myelination in areas exhibiting this pattern (Jones et al., 2013).

Interpreting patterns of diffusion parameters to infer white matter tissue characteristics is largely context dependent. The same patters identified here, in the context of, neurological disorders, traumatic brain injury or when looking at the impact of aging in the elderly indicate different mechanisms are responsible for changes in the diffusion parameters accompanying changes in FA. For example, decreases in MD are observed briefly after stroke due to cell swelling, whereas models of Wallerian degeneration of brain injury indicate tissue degeneration is associated with decreases in FA and increases in RD, with no significant change in MD (Beaulieu, Does, Snyder, & Allen, 1996; Concha, Gross, Wheatley, & Beaulieu, 2006). Decreases in FA and AD in the absence of other changes have been shown to indicate axonal fragmentation, swelling, and organelle accumulation (Song et al., 2003). Therefore, it may be misleading to infer changes in diffusion parameters due to adolescent psychopathology during

development are solely the result of tissue characteristics related to the developing brain. Although this converges with findings from other imaging modalities (functional magnetic resonance imaging and electroencephalography) where functional activity in adolescents with psychopathology resembles patterns found with younger participants in research examining cognitive development. However, one must consider the possibility the changes in these diffusion parameters linked to adolescent psychopathology might reflect other mechanisms (i.e. axonal loss, tissue degeneration) that are not related to development.

Similarities and Differences in Age-Related FA Changes between Clinical and Healthy Adolescents

Age-related white matter changes during adolescence typically show increased FA values with age and this relationship is thought to reflect the increased integrity associated with brain maturation of neural communication specifically underlying emerging functional networks. However, a recent reports examining white matter changes related to cognitive performance (particularly executive control functions) in children and adolescents show increased impairment in cognitive performance related to higher FA values (Lebel et al., 2013; Seghete et al., 2013; Treit et al., 2014). Numerous behavioral studies show executive functioning and cognitive control abilities increases with age. Therefore, and consistent with our findings, it is possible that not all white matter maturation underlying functional maturation is associated with increases in FA.

Cognitive inhibition in a sample of children and adolescents (ages ranging from 5 – 16 years) showed higher FA values in anterior frontal and orbital frontal corpus callosum related to impaired cognitive inhibition (Treit et al., 2014). This relationship held after including age as a covariate. Moreover, and as referred to in the introduction, some investigations of white matter

changes in adolescent psychopathology have shown increases in FA in the clinical group. These findings suggest that the white matter development facilitating function may in cases of psychopathology promote maladaptive alterations in neural communication, thus supporting circuity related to dysfunctional cognitive processes and behavior. The dissociation we observed in the genu of the corpus callosum with CLAs having increased FA with age and HCAs decreased FA with age may be demonstrative of this idea as the CLAs also showed decreased attentional control ability and greater impairment in a paradigm assessing response inhibition (Shafer et al., in prep). Moreover, in CLAs, vACC/vmPFC activity (an area populated with connections from the genu of the corpus callosum) was related to task impairment and increased functional connectivity with the amygdala (a basic emotion processing region), whereas in HCAs this area was related to enhanced task performance and increased functional connectivity with frontal and parietal cognitive control regions (Shafer et al., in prep).

Limitations

There are three main limitations of the current study. First, as a cross-sectional study there are inherent limitations when looking at age-related changes. There is enormous variability in brain development and the best approach for understanding these changes is through longitudinal studies or extremely large sample cross-sectional studies. As such conclusions drawn from smaller sample, cross-sectional examinations of age-related trajectories during development should be made cautiously. In light of this, findings from these designs may be validated through replication. Considering this fact together with the knowledge that research on adolescent psychopathy is limited, it is remains advantageous to investigate such questions even if the sample size is less than desirable. Second, the inability to control for type of medication or medication duration is a potential confound in the current investigation. Finally, the

implementation of a sample specific white matter mask may have eliminated sensitivity to finding differences in areas where white matter (as inferred by good tensor fit) may have existed for one group in certain areas but was reduced in the other group. Future research from our group examining region of interest analysis/tractography will be able to address this issue.

Conclusions

In summary, this study identified general and age-related alterations in white matter microstructure in adolescents with Axis-I affective, attentional and behavioral mental health disorders. First, we found smaller FA values for the clinical compared to healthy adolescents in lobar white matter, white matter involved in inter-hemispheric communication, and white matter important for cortical-cortical and subcortical-cortical connections. Second, we identified diffusivity patterns suggesting differences in white matter microstructure between groups in some areas may be largely due to delayed development (i.e., reduced myelination and/or decreased fiber coherence). Third, we found a clear dissociation between groups in age-related FA changes in the genu of the corpus callosum. This area had increased FA values with increased age the clinical group, but had decreased FA values with increased age in the non-clinical, healthy group.

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Table 7-1. Diagnostic and medication in formation for the 20 clinical adolescents.

Diagnosis	**Number**	**Medication (number of patients)**				
	(M/F)	**Unknown/ None**	**Stimulants**	**Anti-depressants**	**Anti-psychotics**	**Other**
Distress disorders *(MDD, Dysthymia, SP, GAD, PTSD)* co-morbid with one or more following disorders						
Distress disorders and ADHD, PCRP	(2/4)	1/-	4	5 - SSRI	2	-
ADHD, CD, ODD, PCRP, RAD	(4/3)	-/-	2	4 – SSRI	4	1 - BZD
ADHD co-morbid with one or more following disorders						
CD, ODD, PCRP, RAD	(2/2)	-/-	4	2 – SSRI 1 - NDRI	6	-
Others: one or more following disorders						
ODD, PCRP, AD	3 (0/3)	-/2	-	1-SSRI	1	-
Total	20 (8/12)	1/2	10	12 – SSRI 1 - NDRI	13	1 - BZD

AD = Attachment Disorder; ADHD=attention-deficit/Hyperactivity disorder; CD = Conduct Disorder; GAD = Generalized Anxiety Disorder; MDD = Major Depressive Disorder; PTSD = Post Traumatic Stress Disorder; ODD= Oppositional Defiant Disorder, PCRP=Parent-Child Relational Problem; RAD = Reactive Attachment Disorder; SP = Social Phobia; SSRI, selective serotonin reuptake inhibitor; NDRI, norepinephrine-dopamine reuptake inhibitor; BZD, benzodiazepine.

Table 7-2. White Matter Structures with Decreased FA for Clinical Adolescents.

White Matter Structure	Hemi.	MNI Coordinates			Diffusivity Pattern	Cluster Size
		x	y	z		
Clinical < Control FA						
Lobar White Mater						
SFG	L	-16	25	45	1 // 3	40 // 35
CG	R	18	-42	32	1	80
STG	L	-42	-14	-11	1	37
Inter-hemispheric Connections						
Corpus Callosum						
Genu	M	0	25	3	1 // 2 // 3	242 // 41 // 38
	L	-14	35	12	1 // 2	106 // 17
		-11	20	-6	1	34
	R	10	31	3	1	35
		13	23	11	1	96
Body	L	-6	1	24	1 // 3 // 5	194 // 130 // 68
	R	9	7	27	1 // 3	42 // 30
		12	-4	31	1 // 2	71 // 34
		18	-18	34	1 // 2 // 3 // 4	160 // 54 // 75 // 36
Splenium	R	9	-35	11	1	97
		9	-39	21	1 // 3	50 // 33
Subcortical and Cortical Connections						
Association Fibers						
Uncinate Fasciculus	R	39	-1	-19	1 // 2	55 // 32
Projection Fibers						
Corona Radiata						
ACR	L	-23	33	-3	1 // 2 // 3 // 4	264 // 104 // 89 // 57
	R	18	25	-10	1 // 2	90 // 20
SCR	R	28	-23	29	1	54
Internal Capsule						
ALIC	L	-20	10	17	1	37
		-17	4	9	1 // 3	91 // 38
		-20	-2	15	1 // 2 // 3	158 // 62 // 48
PLIC	L	-17	-12	-4	1 // 3	55 // 33
		-20	-22	11	1 // 2	41 // 28
	R	17	-3	6	1 // 2 // 2 // 3 // 4	580 // 218 // 22 // 230 // 79
Cerebral Peduncle	R	13	-16	-7	1 // 2 // 3 // 3	461 // 74 // 33 // 31
Posterior Thalamic Radiation	R	27	-72	12	1	38

Coordinates are reported for the peak voxel from the contrast assessing group differences in FA (i.e., pattern 1). The diffusivity patterns reported for an area have a one-to-one mapping with the reported cluster sizes. That is, the first diffusivity pattern reported for an area was identified in a number voxels corresponding to the first cluster size reported for an area. Diffusivity Patterns: 1 = decreased in FA; 2 = decreased FA and

AD; 3 = decreased FA and increased RD; 4 = decreased FA and AD, and increased RD; 5 = decreased FA and increased RD and MD. SFG, superior frontal gyrus; CG, cingulate gyrus; STG, superior temporal gyrus; ACR, anterior corona radiata; SCR, superior corona radiata; ALIC, anterior limb of the internal capsule; PLIC, posterior limb of the internal capsule; CC, corpus callosum; CP, cerebral peduncle; L, left; R, right; M, midline.

Table 7-3. Similarities in the relationship between FA and age for Healthy and Clinical Adolescents.

White Matter Structure	Hemi.	Pearson r (HC/CA)	p-value (HC/CA)	MNI Coordinates x	y	z	Cluster Size
Positive Correlation Conjunction							
Subcortical and Cortical Connections							
Projection Fibers							
Corona Radiata							
SCR	L.	.52/.49	.02/.03	-22	-5	27	115
PCR	R.	.54/.61	.01/.005	24	-44	29	321
Negative Correlation Conjunction							
Subcortical and Cortical Connections							
Projection Fibers							
Ansa Lenticularis	L.	-.45/-.47	.05/.04	-23	-4	-10	67

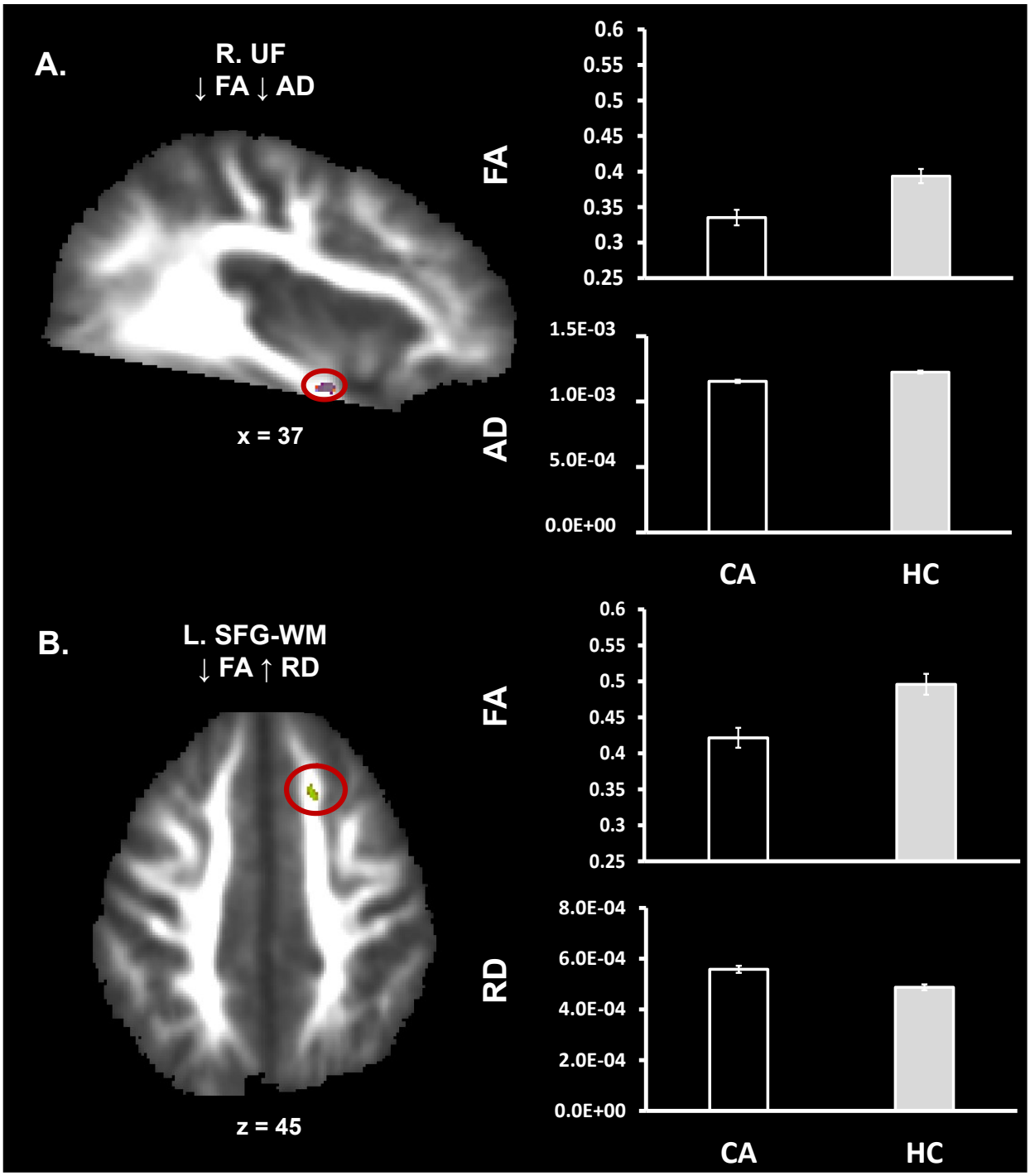
Coordinates are reported for the peak voxel from clusters identified in the conjunction maps created to examine similarities for positive (top) and negative (bottom) correlations between age and FA across groups. The cluster size indicates the area of overlap as identified in the conjunction maps. Pearson r-values and their corresponding p-values are based FA values averaged across the entire cluster. Hemi., hemisphere; HC, healthy control; CA, clinical adolescents; PCR, posterior corona radiata; SCR, superior corona radiata; L., left; R., right.

Table 7-4. Differences in the relationship between FA and age for Healthy and Clinical Adolescents.

White Matter Structure	Hemi.	Pearson r (HC/CA)	p-value (HC/CA)	MNI Coordinates x	y	z	Cluster Size
HC Positive Correlation with Age							
Lobar White Matter							
SFG-WM	L.	.62/-.19	.003/ns	-19	-7	52	217
PrG-WM	L.	.58/.02	.008/ns	-21	-25	50	155
CG-WM	R.	.73/.007	.001/ns	18	-44	31	1609
Inter-hemispheric Connections							
Corpus Callosum							
Splenium	L.	.81/.09	.001/ns	-24	-51	19	785
Subcortical and Cortical Connections							
Projection Fibers							
Corona Radiata							
ACR	R.	.63/.05	.003/ns	20	32	31	211
SCR	L.	.52/.25	.02/ns	-22	-6	27	565
	R.	.60/.23	.005/ns	16	5	42	343
Posterior Thalamic Radiation	R.	.62/-.30	.003/ns	39	-52	7	446
CA Positive Correlation with Age							
Lobar White Matter							
SFG-WM	R.	-.09/.65	ns /.002	22	45	15	579
SOG-WM	R.	-.15/.63	ns /.003	25	-75	24	171
Inter-hemispheric Connections							
Corpus Callosum							
Genu	R.	-.58/.62	.007/.003	13	30	17	205
Body	L.	.17/.66	ns /.001	-15	-1	37	542
	R.	-.24/.58	ns/.007	1	15	16	586
Subcortical and Cortical Connections							
Projection Fibers							
Corona Radiata							
ACR	L.	-.12/.7	ns /.001	-18	36	23	645
ACR/SCR	L.	-.007/.57	ns /.009	-23	17	28	296
	R.	-.04/.57	ns /.008	22	23	24	369
SCR	L.	.15/.74	ns /.001	-23	-2	21	317
		-.15/.62	ns /.003	-20	-22	32	408
	R.	.13/.58	ns /.007	20	0	31	231
Internal Capsule							
PLIC	L.	.21/.75	ns /.001	-22	-13	0	384
Thalamus							
VLA/VLP	R.	-.04/.65	ns /.002	11	-13	-3	511
Association Fibers							
IFOF	L.	.26/.55	ns/.01	-24	18	-10	297
	R.	-.36/.73	ns/.001	26	19	-9	282
SLF	L.	.09/.56	ns /.01	-41	-24	30	237

	R.	-.09/.70	ns /.001	32	-31	28	437
		.13/.55	ns /.01	27	-41	32	389
Sagitall Stratum	L.	-.006/.62	ns /.003	-38	-23	-10	590
	R.	-.1/.71	ns/.001	37	-25	-7	1626
HC Negative Correlation with Age							
Lobar White Matter							
SFG-WM	R.	-.72/-.08	.001/ns	12	12	53	200
Inter-hemispheric Connections							
Corpus Callosum							
Genu	R.	-.59/.37	.006/ns	13	27	15	574
Subcortical and Cortical Connections							
Projection Fibers							
Internal Capsule							
PLIC	R.	-.65/.13	.002/ns	20	-14	-2	170
Posterior Thalamic Radiation	R.	-.64/-.21	.002/ns	34	-64	2	251
Association Fibers							
External Capsule	R.	-.63/.35	.003/ns	30	19	-3	271
		-.71/-.001	.001/ns	30	1	10	519
UF	L.	-.6/.02	.005/ns	-27	-3	-14	256
	R.	-.71/.22	.001/ns	31	-6	-16	319
SLF	R.	-.66/.23	.002/ns	31	-24	29	535
CA Negative Correlation with Age							
Lobar White Matter							
SFG-WM	R.	-.08/-.58	ns/.007	17	-1	54	224
STG-WM	R.	.39/-.7	.09/.001	39	-37	11	872
MTG-WM	L.	.31/-.58	ns/.007	-38	-42	9	340
Subcortical and Cortical Connections							
Projection Fibers							
Corona Radiata							
ACR	L.	-.007/-.71	ns/.001	-26	23	15	727
Internal Capsule							
PLIC	R.	-.17/-.58	ns/.007	25	-12	11	311
Posterior Thalamic Radiation	L.	.31/-.59	ns/.006	-36	-62	1	240

Coordinates are reported for the peak voxel from clusters identified in the conjunction maps created to examine similarities for positive (top) and negative (bottom) correlations between age and FA across groups. The cluster size indicates the area of overlap as identified in the conjunction maps. Pearson r-values and their corresponding p-values are based FA values averaged across the entire cluster. Hemi., hemisphere; HC, healthy control; CA, clinical adolescents; SFG, superior frontal gyrus; CG, cingulate gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; SOG, superior occipital gyrus; PrG, precentral gyrus; UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; IFOF, inferior fronto-occipital fasciculus; ACR, anterior corona radiata; SCR, superior corona radiata; ALIC, anterior limb of the internal capsule; PLIC, posterior limb of the internal capsule; CC, corpus callosum; CP, cerebral peduncle; VLA, anterior ventral lateral thalamus; VLP, posterior ventral lateral thalamus; L, left; R, right; ns, non-significant.


A.
R. UF
↓ FA ↓ AD
x = 37
FA
0.6
0.55
0.5
0.45
0.4
0.35
0.3
0.25
AD
1.5E-03
1.0E-03
5.0E-04
0.0E+00
CA
HC
B.
L. SFG-WM
↓ FA ↑ RD
z = 45
FA
0.6
0.55
0.5
0.45
0.4
0.35
0.3
0.25
RD
8.0E-04
6.0E-04
4.0E-04
2.0E-04
0.0E+00
CA
HC

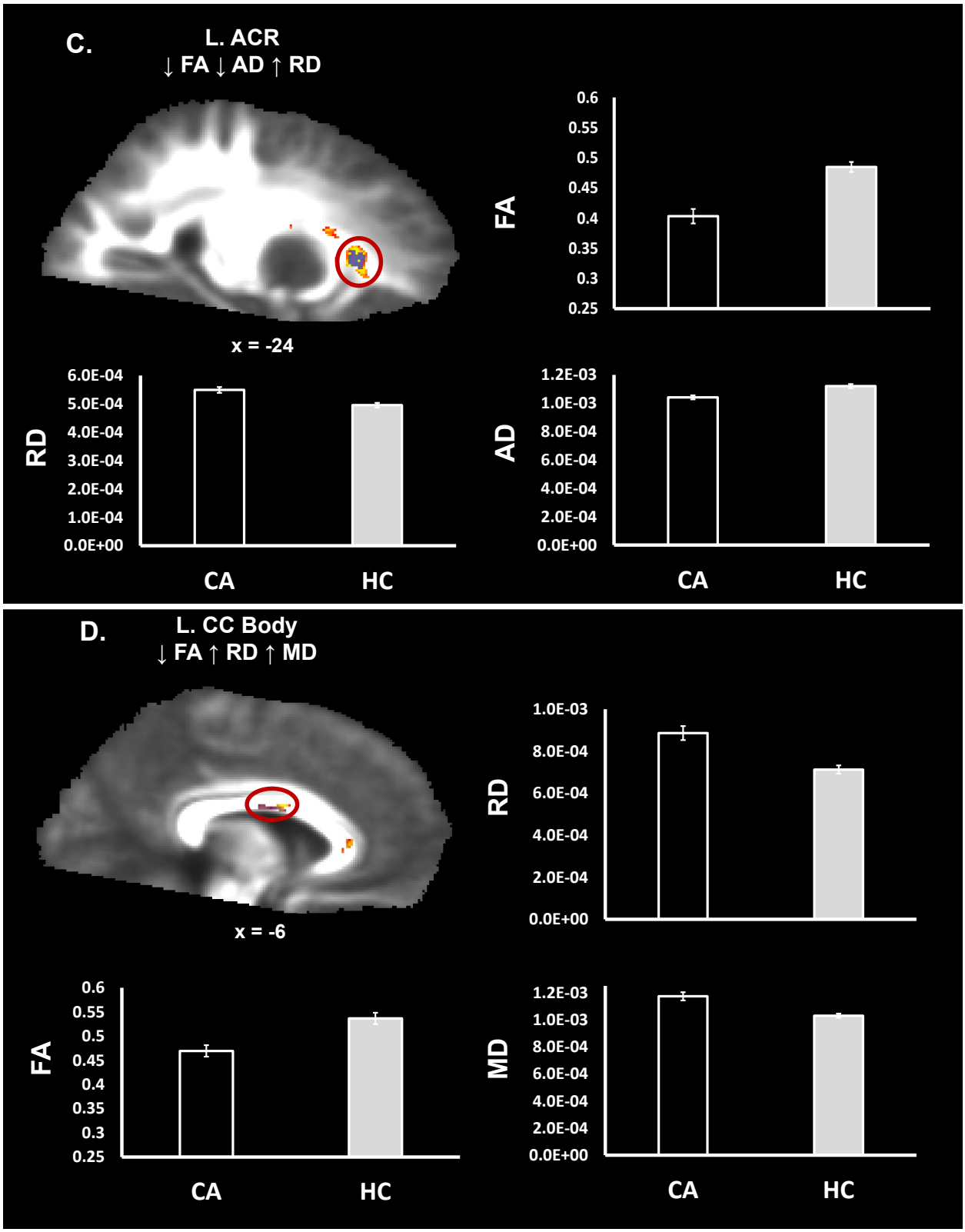


Figure 7-1. Areas showing decreases in FA values for clinical compared to control adolescents. Each area displayed is representative of one of the diffusivity patterns identified when considering axial

(AD), radial (RD), and mean (MD) diffusivities in addition significant differences in FA values. A) Decreased FA and AD (purple blob) in the right uncinate fasciculus (UF). B) Decreased FA and increased RD (green blob) in left superior frontal gyrus white matter (SFG-WM). C) Decreased FA and AD, and increased RD (blue blob) in left anterior corona radiata. D) Decreased FA, and increased RD and MD in the left body of the corpus callosum (CC). All colored blobs are overlaid onto red blobs that show areas of decreased FA for clinical adolescents. Images are displayed in radiological convention (right side of the axial image corresponds to left side of brain). The activation maps are superimposed on the averaged FA image.

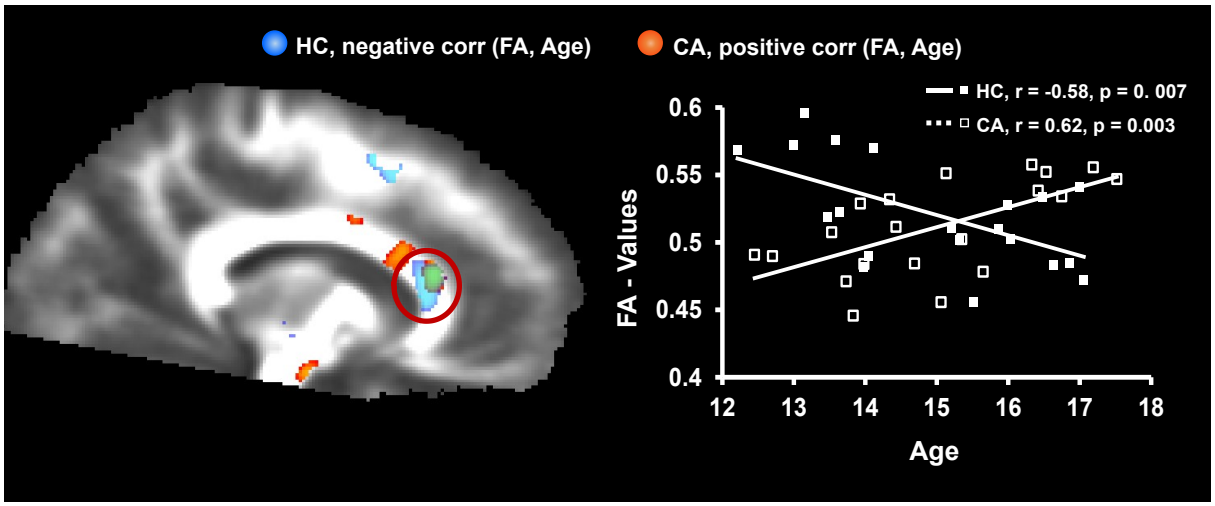


Figure 7-2. Genu of the Corpus Callosum Shows Different Developmental Trajectories for FA in Clinical Adolescents. In the genu of the corpus callosum, increased FA values were associated with increased age in the clinical group (red blobs), whereas for the control group, decreased FA values were associated with increased age (blue blobs). Overlap between the positive and negative correlation maps is indicated by green blob. The r-values were calculated by correlating age with the average of the FA values as extracted from the red blob for both clinical and healthy adolescents. The activation maps are superimposed on the averaged FA image.

CHAPTER 8

GENERAL DISCUSSION

Review of the main findings

The overarching goal of the present work was to address open questions in the literature concerning emotional and cognitive processing in healthy and clinical populations. Emotional disturbances and/or turmoil in healthy and clinical individuals can impair functioning in daily life. Understanding external (e.g., the degree of emotional and cognitive challenge present) and internal (e.g., neuronal functioning and the presence of psychopathology) factors that influence the susceptibility to emotional distraction and/or impaired functioning in general (e.g., impulsivity) is critical in being able to effectively treat mental health disorders. This is especially important as the impact of many mental health disorders where emotional and cognitive processes are impaired may be so extreme that it debilitates individuals from living a productive life and contributing to society in a continuously meaningful way. The work presented in this thesis used neuroimaging techniques to provide novel insights on both external and internal factors influencing susceptibility to emotional distraction in general and through its impact on goal-oriented cognition. Moreover, the current work not only focused on the immediate impact of emotional distraction, but also its long-term impact on memory. Translating between the immediate effects of emotional distraction and its long-term consequences (i.e., emotional memory) as well as an increased understanding of emotional memory in general, is incredibly important as both aspects are impacted many mental health disorders.

In this work three different neuroimaging techniques and behavioral paradigms were used across two large studies that each focused on unresolved issues concerning aspects related to emotion-cognition interactions. Two of the neuroimaging techniques employed were functional (ERP and fMRI) allowing inferences to be made about the neural mechanisms associated with behavior. One offered better information about *when* typical and atypical alterations in emotional

and cognitive processes occurred (i.e., EEG/ERP). The other provided better information about *where* in the brain typical and atypical alterations in emotional and cognitive processes were taking place (i.e., fMRI). The third neuroimaging technique, DTI, examined structural changes in the brain, allowing inferences to be made about the quality of white matter pathways important for neural communication and information transfer within the brain.

The three main behavioral paradigms used in the present work were; the attentional capture paradigm, the subsequent memory paradigm, and the modified emotional oddball paradigm. First, the attentional capture paradigm was used in conjunction with fMRI to examine the immediate impact of emotion on cognition. The findings of which are reported in *Issue 1* of study one. Next, in *Issue II* of study one, the subsequent memory paradigm was used in combination with the attentional capture paradigm and fMRI to examine factors linking the immediate and long-term impact of emotion on cognition. Then, in *Issue III* of study one, the subsequent memory paradigm was employed again in conjunction with fMRI to delineate memory processes involved in the memory-enhancing effect of emotion at retrieval. Then, study two implemented the modified emotional oddball paradigm to identify alterations in emotional and cognitive processes in adolescent psychopathology. First, in *Issue IV*, ERPs were used to examine differences in general emotion processing and emotion-cognition interactions between clinical and healthy adolescents. Second, in *Issue V*, fMRI was used to investigate the neural correlates associated increased impulsivity in adolescent psychopathology. Lastly, *Issue VI* implemented DTI to examine structural (i.e., white matter) differences that could be potentially related to the functional differences observed between clinical and non-clinical groups. Below, I provide a summary of the main findings for each issue investigated, mention emergent areas of

exploration based on the current findings, and discuss the overall limitations and significance of the present work.

Study One: An fMRI Investigation of the Immediate and Delayed Impact of Emotional Distraction in a Sample of Healthy, Young Adults.

Issue I: The Impact of Emotional Distraction on Perception: The Role of Attentional Load and Emotional Charge.

Findings from *Issue I* made a significant contribution to affective neuroscience by reconciling opposing theories regarding emotion-cognition interactions. While the traditional theories (Vuilleumier, Armony, Driver, & Dolan, 2001) suggest that processing of emotion occurs free from the constraints of attention, the competing theories (Pessoa, McKenna, Gutierrez, & Ungerleider, 2002) suggests that processing of emotion, like all other stimuli in our environment, depends on the availability of attentional resources. Unlike investigations of emotion-attention interactions providing support for these opposing theories that have mainly emphasized the emotional or the attentional component (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003; Mitchell et al., 2007; Morris, Ohman, & Dolan, 1999; Pessoa et al., 2002; Pessoa, Padmala, & Morland, 2005; Vuilleumier et al., 2001), the findings reported here reconciled these opposing theories by manipulating the degree of both emotional and cognitive challenge in determining attention's influence on emotion processing. This approach allowed for dissociation of brain areas susceptible to attention-dependent manipulations of emotion processing from those that were invariant in their response to emotion. The prefrontal cortex was linked to a reduction in or enhancement of engagement in response to emotion depending on attention availability, whereas, the amygdala was involved in the processing of emotion regardless of attention availability. Furthermore, findings from this investigation identified brain regions (dmPFC,

vlPFC) linked to enhanced detrimental impact of emotional distraction, and brain regions (dACC, LOC) linked to a reduction in the negative impact of emotional distraction on task performance. Collectively, findings from this investigation contribute to advancing current theories of emotion-cognition interactions and highlight the importance of manipulating both emotional and cognitive challenge when examining the interplay between emotion and cognition.

Importantly, there are two immediately obvious emerging areas of investigation based on findings from this issue. First, to identify factors important for resilience or for increased susceptibility to psychopathology the role of individual differences in aspects related to personality, cognitive control or emotional intelligence in producing the differences in mean activity should be examined. Interestingly, preliminary evidence shows the relationship between individual differences in and susceptibility to emotional distraction is context dependent (Shafer & Dolcos, 2010). Specifically, traits associated with reduced attentional control resulted in greater susceptibility when more resources were available for distraction and traits associated with heightened inhibition/withdrawal system sensitivity resulted in greater susceptibility to distraction when less resources were available for distraction. Second, the current issue focused on the impact of emotional and cognitive challenge in brain regions comprising an 'emotional network' (i.e., areas sensitive to modulation by emotion such that there is increased responsivity to emotion). It would be informative to examine the interplay between emotional and cognitive challenge in brain regions comprising a 'cognitive control network' (i.e., areas showing increased responsivity to increases in perceptual load).

Issue II: The Impact of Emotional Distraction on Memory: Linking the Immediate and Delayed Influence of Emotional Distraction on Cognition.

Findings from Issue II provide evidence for a direct link between the immediate and long-term impact of emotional distraction during a lower-level perceptual task under conditions of limited resource availability during encoding, and an indirect link under conditions of increased resource availability. Consistent with a role of automatic mechanisms (Ritchey, LaBar, & Cabeza, 2011) linking these opposing effects, AMY-HC activity was common to both the immediate/impairing effect of emotional distraction and the long-term/enhancing impact of emotion on memory. Furthermore, brain regions were identified as being specifically susceptible to emotional modulation during distraction or memory formation, with certain regions (Medial Frontal Gyrus, PrCG, STG, MOG) linked to the immediate impact on perceptual performance and others (SPL) to the long-term impact of emotion on memory. In addition, the engagement of attention-mediated mechanisms (Dolcos & McCarthy, 2006; Kensinger & Corkin, 2004) when more resources were available during encoding, diminished the impact of emotion on memory and the involvement of automatic mechanisms. These findings demonstrate that the relationship between emotional distraction and memory is context dependent and that specific brain regions may be more or less susceptible to the direction of emotional modulation (increased or decreased), depending on the task manipulation and processes investigated. Understanding the mechanisms linking emotional distraction and memory offers important insight into clinical conditions, such as depression and anxiety, where both of these effects are dysfunctionally exacerbated.

Although findings from this issue were critical at identifying factors establishing a direct or indirect link between emotional distraction and memory, and in identifying the neural mechanisms associated with forming a direct link; it will be important for future work to identify the neural mechanisms associated with the indirect relationship. That is, what brain regions come

'online' or go 'offline' to allow a boost in memory for neutral distraction so that there is no longer a memory-enhancing effect of emotion when more resources are available for distraction?

Issue III: The Long-Term Impact of Emotion on Cognition: Dissociating Memory Processes Involved in the Memory-Enhancing Effect of Emotion.

Findings from *Issue III* expanded our understanding of the neural mechanisms involved in the memory-enhancing effect of emotion at retrieval. First, findings distinguished between MTL activity related to two memory processes (encoding and retrieval) as they were involved in the memory-enhancing effect of emotion at retrieval. Consistent with extant research, greater activity related to the successful retrieval of emotional relative to neutral memories was identified bilaterally throughout MTL structures [AMY, HC, and PHC (Dolcos, LaBar, & Cabeza, 2005; Kensinger & Schacter, 2005)]. The AMY showed the largest overlap between memory processes related to both encoding and retrieval, as right AMY identified during retrieval was accounted for by encoding-related activity. However, the left AMY showed an exclusive relationship with the memory-enhancing effect of emotion during retrieval. There was little overlap between HC and PHC regions for encoding and retrieval activity related to the memory-enhancing effect of emotion. Second, findings show that sub-regions within MTL structures had different temporal and spatial dissociations in the BOLD response for the memory enhancement of emotional or neutral items. An earlier and more anteriorly spread response (in left AMY and bilateral HC and PHC) was linked to greater emotional retrieval success, whereas a later and more posteriorly localized response (in right posterior PHC) was linked to greater neutral retrieval success (Kensinger & Schacter, 2005; Sharot, Delgado, & Phelps, 2004). These findings demonstrate that retrieval activity related to the memory-enhancing effect of emotion can be dissociated and linked to different memory operations. Furthermore, these findings shed

light on the neural mechanisms of emotional memory retrieval in healthy behavior which is important for understanding alterations in these processes associated with affective mental health disorders were unwanted, intrusive recollection of past events becomes debilitating and impairs functioning. Future work in this area can add specificity to the current findings through high resolution functional imaging of the MTL in combination with the use of anatomical regions of interest in MTL structures and subfields to offer more precise boundaries for BOLD activity. Additionally, it will be important to continue the theme of examining the effect of emotional modulation by cognitive challenge, however with the focus here on response in the MTL at retrieval due to modulation during encoding.

Study Two: A Multi-modal Imaging Investigation of Functional and Structural Alternations Associated with Adolescent Psychopathology.

Issue IV: The Impact of Emotional Distraction on Goal-Oriented Target Processing in Adolescent Psychopathology - ERP Evidence

Findings from *Issue IV* begin to elucidate alterations in emotion-cognition interactions linked to adolescent psychopathology. First, similarities and differences in the data were found between the clinical and non-clinical adolescent groups. While behaviorally the groups responded similarly to emotional distraction, early (P100) and late (LPP) ERP markers of stimulus processing showed increased processing of emotional distraction (i.e., fearful) for the clinical group. Furthermore, emotional modulation of target processing was found for the clinical group as ERP markers of attention showed increased (P300) and sustained (LPP) amplitude to targets that were preceded by emotional distracters. Taken together, these findings show that similar to adults (Wang, Krishnan, et al., 2008; Wang, LaBar, et al., 2008) both affective and cognitive dysfunction are involved in adolescents psychopathology as the clinical group

displayed increased sensitivity to emotional distraction and emotional modulation of attentional-control processes, respectively.

Issue V: Neural Correlates of Impaired Response Inhibition in Adolescent Psychopathology – fMRI Evidence

Findings from *Issue V* provide novel information on the neural mechanisms related to the increased impulsivity found in adolescent psychopathology (van Velzen, Vriend, de Wit, & van den Heuvel, 2014). First, adolescents with Axis-I affective, attentional, and behavioral mental health disorders had decreased engagement of frontal and parietal brain regions during target processing. Second, vACC engagement during target processing was shown to have a different relationship with individual differences in attentional control and task performance for the clinical and non-clinical groups. In the clinical group, the engagement of this region was linked to decreased attentional control and impaired task performance, whereas in the non-clinical group activity was linked to increased attentional control and enhanced task performance. Third, synchronicity between brain regions engaged during target processing differed between clinical and non-clinical groups. During target processing, the clinical group had increased functional connectivity between ventral structures that were also involved in general distracter processing. However, the non-clinical group had increased functional connectivity between dorsal frontal and parietal regions known to be important in cognitive control. These findings suggest that the increased impulsivity observed in adolescent psychopathology is related to cognitive dysfunction, as indicated by overall decreased involvement of frontal and parietal cognitive control regions and in decreased synchronicity between them. Furthermore, these findings suggest that increased impulsivity may also be related to affective dysregulation (perhaps due to

the cognitive dysfunction), as ventral structures typically involved in distracter processing had increased functional connectivity during target processing in the clinical group.

Issue VI: Alterations in White Matter Microstructure Associated with Adolescent Psychopathology – DTI Evidence

Findings from *Issue VI* provide additional evidence that structural brain changes are evident in adolescent psychopathology (Diwadkar & Keshavan, 2006). General and age-related differences in white matter microstructure were identified between clinical and non-clinical groups. First, smaller FA values were found throughout a number of white matter structures sub-serving different functions in neural communication. These included lobar white matter, callosal white matter involved in inter-hemispheric communication, and white matter important for cortical-cortical (association fibers) and subcortical-cortical (projection fibers) connections. Second, in some areas showing decreases in FA in the clinical group, differences in other diffusivity parameters were also found, indicating that either reduced myelination or decreased fiber coherence may be responsible for the smaller FA in those areas. Third, a clear dissociation in the genu between groups in age-related FA changes was identified such that the clinical group had increased FA values with age and the non-clinical group had decreased FA values age. A result that is consistent with research examining the role of individual differences in the relationship between FA and executive functioning in this region, such that increased FA is related to behavioral deficits (Treit, Chen, Rasmussen, & Beaulieu, 2014). Taken together, these findings shed light on structural brain changes that may be associated with the functional changes found in *Issues IV* and *V*, and show different developmental trajectories in white matter microstructure in adolescent psychopathology.

When considering the findings from all three issues in study two together, three main lines of investigation emerge. First, based on findings in the fMRI data, it will be important to investigate event-related oscillations and differences in coherence between clinical and non-clinical samples in the EEG data. Second, based on the ERP findings, it will be important to investigate between group differences in the emotional modulation of cognitive control processes involved in goal-oriented and sustained attention as well as in response inhibition in the fMRI data. Third, based on findings from the ERP, fMRI, and DTI data, it will be important to make stronger connections between the structural and functional differences observed individually in each modality. Regressing behavioral and functional differences against structural data, or regressing behavioral and structural differences against functional data will allow for the identification of unified constructs concerning neuronal integrity and functioning related to behavior and adolescent psychopathology. One readily apparent integrating aspect concerns examining how the integrity of tracts passing through the genu of the corpus callosum into the medial frontal cortex influence activity in this area of cortex, and then how the timing, amplitude, and coherence of electrical activity are consequently modified as a result of the relationship between FA and BOLD measurements.

Limitations

An in depth discussion on the limitations related to each empirical chapter in the present work may be found at the end of each chapter. However, the main limitations of the techniques implemented and in some instances the context in which they were used, thus limitations threaded throughout multiple sections of the work, as well as those concerning the overall integrity of the dissertation have yet to be discussed and will be so here. First, there has been cause for concern regarding the use of correlations with brain imaging data (as was done in

Chapters 2, 3, 6, and 7). It is now well known that this type of analysis in brain imaging data can lead to spurious relationships and erroneous interpretations (Vul, Harris, Winkielman, & Pashler, 2009). Large sample sizes used in conjunction with appropriate analytical approaches/logic (Liebermann, Berkman, & Wager, 2009) and correction for multiple comparisons is the ideal combatant for handling these concerns. While the chapters in which correlation analyses were applied would have benefited from a larger sample size (as with most brain imaging studies in the last two decades), appropriate measures were taken to ensure correct analytical approaches and proper correction were applied.

Second, some readers make take opposition with the particularly low sample sizes used in investigating some of the issues in the thesis (i.e., chapters 3 and 5). Although, this concern was individually recognized in chapters 3 and 5, I will restate here that even though the small sample sizes in these chapters precluded the ability to draw more concrete interpretations and conclusions from the data, it nevertheless allowed for an initial exploration of these issues. An initial exploration that resulted in important contributions in the cognitive neuroscience of emotional memory and in the clinical realm regarding adolescent psychopathology where imaging studies are scarce.

Lastly, one could point to the large scope of the work comprising this dissertation as a limitation. It is true that the 'typical' dissertation involves a more linear approach, with research investigating one specific cognitive or psychological phenomenon within the same population or across populations. I address the readers with this concern with two main points. First, from the larger perspective of understanding how the human brain relates to the human mind and behavior, emotion and cognition, function and structure are inseparable. That is, one of these cannot be accurately understood without the consideration of the other. As is also the case with

healthy (typical) versus clinical (atypical) brain functioning. Maladaptive alterations in processing that lead to pathology cannot be identified nor understood when removed from the context of a control condition. In this regard, the current dissertation offers a multifaceted approach to understanding the neural correlates of behavior related emotion and cognition that considers these integral aspects of brain function. Second, technological advances have afforded cognitive neuroscientists an unprecedented opportunity in examining brain function in the intact human brain. Multi-modal imaging is an essential and potentially unavoidable avenue for cognitive neuroscientists as pieces of the puzzle currently provided by separate lines of neuroimaging work are integrated to allow for a unifying explanation of neuronal functioning. To that end, the work presented in this thesis is near the cutting edge, presenting a multi-modal imaging approach to examining differences in function and structure related to adolescent psychopathology. Although the findings reported here barely scratch the surface on the type of information multi-modal datasets can offer, these findings have laid the foundation that is necessary for the next order of integration (i.e., constraining the analysis for one modality by parameters extracted from other modalities) to be performed on this dataset and properly interpreted.

Summary

The present work offers novel insights that allow for an increased understanding in brain function, and in the relationship between brain function and behavioral outcomes in healthy functioning and adolescent psychopathology. More specifically, the first part of the present work (study one, *Issues I-III*) provided contributions to furthering the cognitive neuroscience of emotion and emotional memory by; (i) reconciling two competing theories on the interaction between emotion and attention, (ii) identifying factors linking the immediate, impairing and

long-term, enhancing impact of emotion on cognition, and (iii) showing that brain activity related to the memory-enhancing effect of emotion at retrieval could be delineated to reveal the involvement of different memory operations occurring during retrieval.

The second part of the present work (study two, Issues IV-VI) provided contributions to clinical neuroscience and pediatric neuroimaging by; (i) providing ERP evidence of increased susceptibility to emotional distraction and emotional modulation of attentional control processes for clinical adolescents, (ii) providing fMRI evidence of malfunctional cognitive control and affective networks during target processing for clinical adolescents, and (iii) providing DTI evidence that differences in white matter microstructure and in the developmental trajectory of white matter are part of neuronal sequela associated with adolescent psychopathology.

Integrating findings across the two studies shows that understanding the engagement of and reciprocity between two overarching neural systems in the brain (i.e., the dorsal-executive and ventral-affective systems) is the crux of understanding how emotion-cognition interactions influence behavior. Findings from studies one and two show that regions and networks largely residing within the dorsal-executive system are important for maintaining goal-oriented processing in the presence of external (e.g., exogenous emotional stimuli) or internal (e.g., individual differences, presence of psychopathology) factors linked to the likelihood of emotional distraction. Whereas, those within the ventral-affective system, while automatically engaged by emotional stimuli that offer a necessary amount of emotional challenge may in the case of the certain psychiatric conditions, have a faulty on/off switch resulting in a consistent engagement and therefore continued dampening of dorsal-executive system responsivity.

Significance

Many different aspects of information processing are altered in mental health disorders. It would be unique for impairment to be limited to only one process. For instance, individuals with post-traumatic stress disorder suffer from increased awareness of aversive, emotionally relevant stimuli in their environment as well as intrusive, unwanted recollection of past emotionally negative memories. Of course these outcomes are not mutually exclusive, but extant research examining the corresponding brain mechanisms has largely approached these issues in isolation. Paramount for understanding how dysfunction is truly embedded in the brain, study one not only considers how processes are individually impacted by emotion, but also how the impact of emotion on one process influences the impact of emotion on another process.

Importantly, findings from Study Two show overarching similarities in maladaptive alterations in emotional and cognitive processes in adolescents with multiple Axis-I diagnoses. Therefore, therapeutic interventions acting on these processes where similar maladaptive alterations were found (e.g., cognitive control mechanisms) may alleviate symptoms across a number of disorders present during adolescence. Moreover, it will be interesting for future research to determine if therapeutic interventions that impact functional outcomes also reduce or eliminate differences in brain structure and function between clinical and non-clinical individuals.

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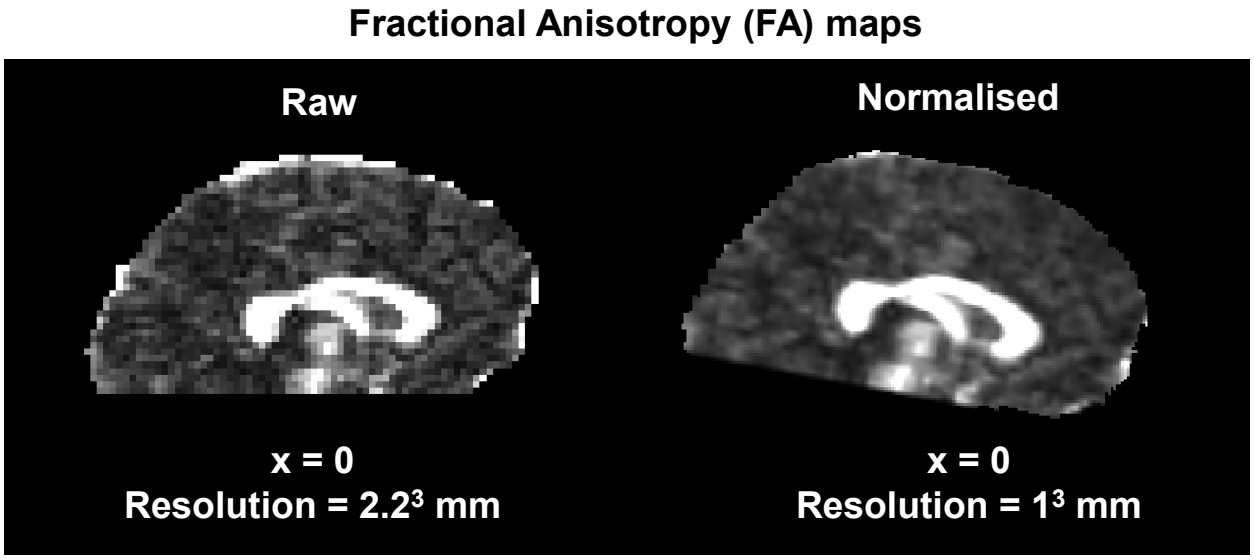
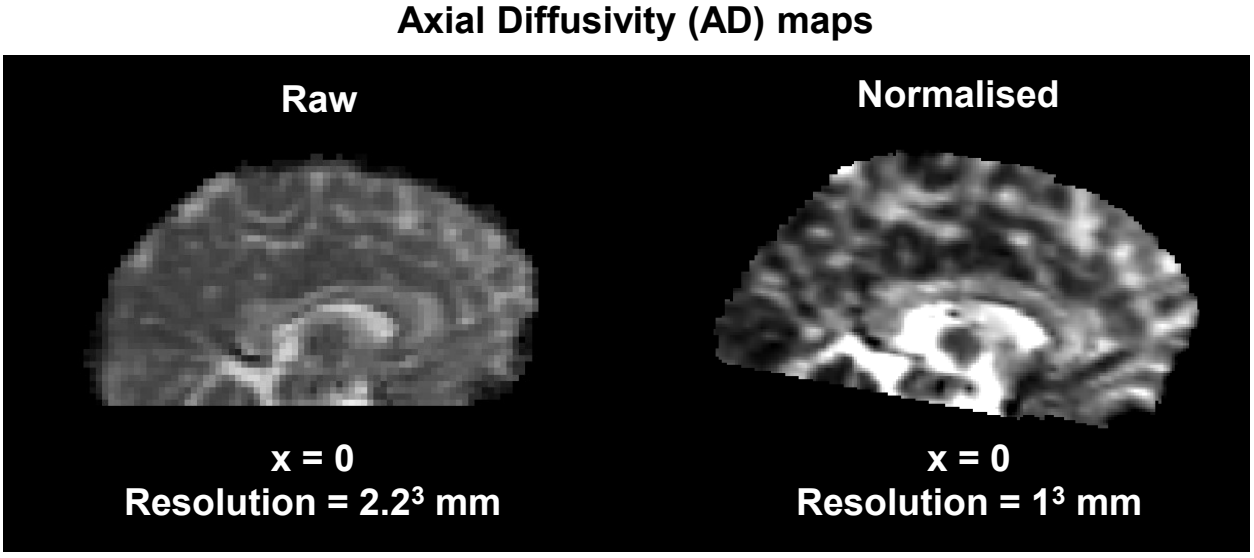
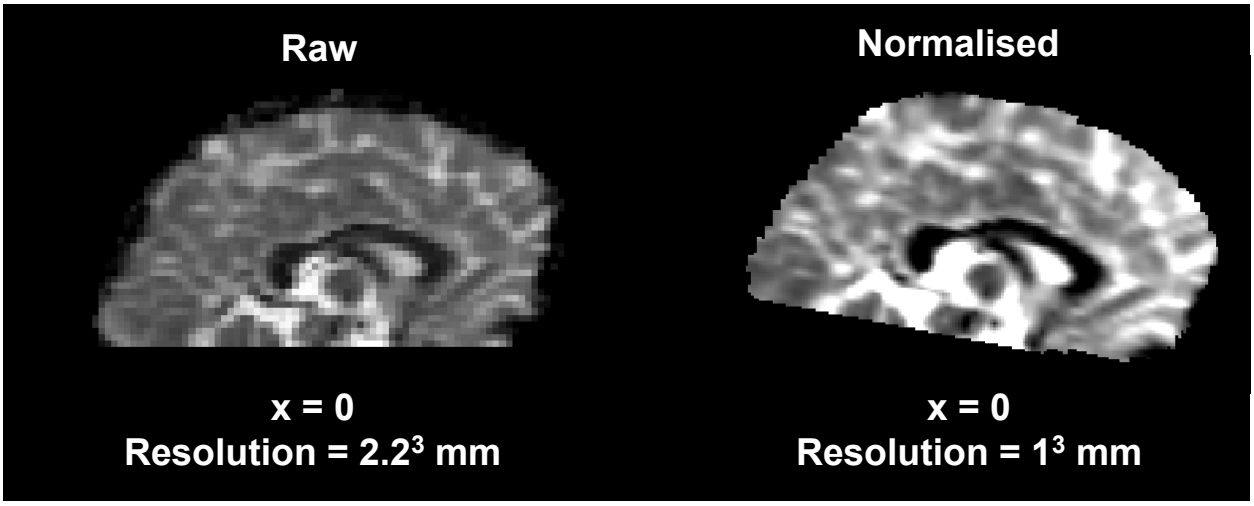
Appendix A: Raw and Normalised Diffusion Tensor Data from a Representative Subject





Radial Diffusivity (RD) maps



Mean Diffusivity (MD) maps