Non-verbal cognitive domain functions positively associate with mildly elevated fasting blood glucose in individuals presenting with a psychotic illness

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Master of Science

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Abstract

Background: The metabolic syndrome (MetS) is a cluster of biological parameters that have been identified as significant risk factors in the development of cardiovascular disease. The relevance of MetS to the psychiatric population has been demonstrated in that having severe mental illness (SMI) itself and also being prescribed antipsychotic medications contribute to the development of MetS. A review of published investigations of non-geriatric general populations suggested that memory, executive functioning, processing speed, and general intellect may be affected by having MetS, with specific MetS factors appearing to correlate with domain-specific cognitive changes. However, the non-geriatric studies tended to sample older populations and thus remain limited with respect to generalization to children, adolescents and young adults.

This study is an exploration of the relationship between MetS and cognitive functioning in a younger population with a psychotic illness. Based on a review of the literature, we hypothesized that individuals with a psychotic illness and meeting criteria for a diagnosis of MetS would have increased cognitive dysfunction in one or more domains, in addition to the effects of having a psychotic illness alone. Additionally, we expected impairment in glucose regulation to be associated with impairment of attention and processing speed, and obesity to be associated with impairments in attention, working memory, and visuospatial skills.

Methods: Individuals presenting with early psychosis (having less than one year of treatment) to the Edmonton Early Psychosis Intervention Clinic in Edmonton, Alberta were assessed with

the MATRICS Consensus Cognitive Battery (MCCB). Clinical assessment also included an evaluation of the factors of MetS as defined by the National Cholesterol Education Programs Adult Treatment Panel III (NCEP-ATP III) criteria. Following an exploratory analysis, linear regression analysis was used to identify possible significant relationships between discrete markers of MetS, such as fasting blood glucose, and specific cognitive domains.

Results: As only two individuals met criteria for MetS, we moved to analysis of discrete markers of MetS and specific cognitive assessments. Fasting blood glucose levels were positively associated with spatial working memory (Wechsler Memory Scale-III: Spatial Span) ($\beta = 0.33$; $t = 2.36$; $p = 0.02$), recall of figures (Brief Visuospatial Memory Test - Revised) ($\beta = 0.30$; $t = 2.15$; $p = 0.04$), and a measure of reasoning and problem solving (Neuropsychological Assessment Battery ®: Mazes) ($\beta = 0.34$; $t = 2.41$; $p = 0.02$). Covariates, such as occupational status, socioeconomic status, years of education, cannabis use, and medication effects did not appear to exert any significant effect on these relationships.

Discussion: This analysis demonstrated that fasting blood glucose values were generally within the normal range in this young sample of individuals suffering a first episode of psychosis, and not associated with measures of sustained attention or processing speed. Fasting blood glucose values were, however, directly associated with performance on several non-verbal tasks sensitive to spatial working memory, learning and memory of designs, and executive skills related to reasoning and problem solving with spatial materials. This relationship was not predicted, but the consistency across non-verbal instruments suggests a potentially reliable effect that may implicate relatively circumscribed cerebral effects of glucose in relation to

relevant neuroanatomy, and to the shifting pattern of cerebral blood flow during cognitive tasks. Although provocative, replication will be necessary to gain confidence in the stability of this result and the validity of inferences regarding potential mechanisms that might underlie this association.

Keywords: Cognition, spatial working memory, non-verbal memory, reasoning and problem solving, MATRICS, MCCB, metabolic syndrome, glucose, psychosis.

Preface

This thesis is an original work by Dr. Sudhakar Sivapalan. The larger study, of which this thesis is a part, received ethics approval from the University of Alberta Health Research Ethics Board, Project Name "Rate of New Onset Metabolic Syndromes in First Episode Psychosis: A historical review of records from the Edmonton Early Psychosis Intervention Clinic", P.I.: Dr. Scot E Purdon, No. Pro00039220, April 20, 2015.

Dr. Sivapalan was the primary author of the two included articles. He was involved in the design of the study, contributed to the ethics application, was responsible for the literature review (including identification and review of included articles), and conducted the analysis of the data presented. The collection of the data was obtained through the clinical services at Alberta Hospital Edmonton Neuropsychology Department, provided by Dr. V. Newton, Dr. S. E. Purdon, Ms. B. Majeau, and Ms. C. Bolt.

The literature review, "Examining the relationships between metabolic syndrome, cognitive dysfunction, and severe mental illness - a literature review" is in submission to the Journal of Psychiatric Research. Dr. K. J. Aitchison and Dr. S. E. Purdon contributed in the role of providing significant review and feedback regarding the manuscript.

The specific investigation, "Non-verbal cognitive domain functions positively associate with mildly elevated fasting blood glucose in individuals presenting with a psychotic illness" is in preparation for submission to the Canadian Journal of Psychiatry. Dr. K. J. Aitchison and Dr. S. E. Purdon contributed in the role of providing significant review and feedback regarding the

manuscript. Dr. S. E. Purdon further contributed through his role in data collection along with Dr. V. Newton, Ms. B. Majeau, and Ms. C. Bolt.

Acknowledgements

I would like to sincerely thank my primary supervisors, Drs. Katherine J. Aitchison and Scot E. Purdon for their time and expert guidance that they have provided to me over these past years. I would like further to thank them for including me in the clinical work at the Edmonton Early Psychosis Intervention Clinic, Edmonton, Alberta, which has allowed me to better appreciate the clinical relevance of this research. A further thank you to Dr. Aitchison for the flexibility and unwavering support that she has provided to me, allowing me to conduct this research on a part-time basis. I would like to thank Dr. Purdon for his insight and assistance with respect to the data analysis and for providing access to this data. I would also like to thank Dr. Glen Baker for his advice and support as a member of my committee and make a further thanks to Dr. Caroline Richard for serving as an examiner in my thesis defence.

Thank you to the University of Alberta Psychiatry Resident Research Program, the Department of Psychiatry, and Alberta Health Services for their support, financial and otherwise, during my time as a resident. Included in this are my resident colleagues (current and former), and my various preceptors and supervisors. I would also like to thank the members of the team in the Aitchison Lab who helped me see another side to conducting research.

Last, but certainly not least, I wish to thank my wife, family, and other friends, who have been steadfast in their support throughout this endeavor.

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Abbreviations

BACS – Brief Assessment of Cognition in Schizophrenia

BMI – body mass index

BVMT-R – Brief Visuospatial Memory Test - Revised

CPT-IP – Continuous Performance Test - Identical Pairs

CRP – C-reactive protein

DSM IV-TR – Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision

DSM 5 – Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

EEPIC – Edmonton Early Psychosis Intervention Clinic

HDL cholesterol – high density lipoprotein cholesterol

HTN – hypertension

HVLT-R – Hopkins Verbal Learning Test – Revised

IDF – International Diabetes Foundation

IGT – impaired glucose tolerance

LNS – Letter-Number Span

MATRICS – Measurement and Treatment Research to Improve Cognition in Schizophrenia

MCCB – MATRICS Consensus Cognitive Battery

MetS – metabolic syndrome

NAB – Neuropsychological Assessment Battery

NCEP-ATP III - National Cholesterol Education Programs Adult Treatment Panel III

SES – socio-economic status

SMI – severe mental illness

TMT-A and -B– Trail Making Test: Part A and Part B

WMS-III – Wechsler Memory Scale, 3rd Edition

1. Introduction

Metabolic syndrome (MetS) is a grouping of medical conditions that are cardiovascular risk factors. These include obesity, lipid metabolism abnormalities (decreased serum high-density lipoprotein (HDL) cholesterol levels or elevated serum triglyceride levels), hypertension (HTN), and insulin resistance. In individuals with severe mental illness (SMI), such as schizophrenia and bipolar disorder, MetS is one of the leading contributors to increased mortality and morbidity. For individuals with schizophrenia, the risk of cardiovascular disease is two to three times higher when compared to the general population, with subsequent disparities in accessing appropriate health care (De Hert et al., 2011). As such, characterising this morbidity is important to the management of individuals with SMI, as early interventions may have positive implications over the course of illness.

MetS has been defined in several ways over the years; the most common definitions include the ones provided by the National Cholesterol Education Programs Adult Treatment Panel III (NCEP-ATP III) (2002), and the International Diabetes Foundation (IDF) in 2005 and 2007, with harmonised criteria being proposed in 2009 (Alberti et al., 2005; Alberti et al., 2009; Zimmet et al., 2007). Regardless of the specific definition, MetS has long been associated with SMI through not entirely independent connections - due to the use of antipsychotic medications and due to having SMI itself. Individually, medication, and especially the atypical antipsychotics, has been linked to weight gain, and this in turn may lead to insulin resistance and dysglycemia (Newcomer, 2005). A recent 2014 study showed that both typical and atypical antipsychotics are associated with weight gain, and the latter also seemed to have a positive

relationship with duration of medication exposure (Bak et al., 2014). Another 2014 study suggested that obesity itself was related to SMI, and that other factors of MetS appear to be related to medication use (Correll et al., 2014).

One of the factors that appears to affect the medical care of individuals with SMI is that even at the time of presentation, individuals with SMI can have cognitive deficits up to three standard deviations below that of the general population (Addington et al., 2003; Bilder et al., 2000; Fitzgerald et al., 2004). To understand that statistic, it is important to appreciate the concept of cognition. This concept dates back over twenty-four centuries and has continued to evolve with increased investigation and understanding of the functioning of the human brain. The DSM-5 (2013) describes several cognitive domains: language, learning and memory, perceptual-motor function, executive function, complex attention, and social cognition. Various cognitive assessment batteries have been developed to investigate cognitive functioning in individuals with SMI such as the MATRICS Consensus Cognitive Battery (MCCB) which investigates the following domains: information processing, attention/vigilance, working memory, learning and memory, reasoning and problem solving, and social cognition (Green and Nuechterlein, 2004; Kern et al., 2008; Nuechterlein et al., 2008). A more in depth description of the domains follows in Chapter 2.

Cognition is a complex set of processes and our understanding of them continues to evolve. It has been suggested that the cognitive deficits experienced by individuals with SMI may be related independently both to having SMI and to MetS, with a number of studies suggesting that individuals with SMI and MetS have diminished cognitive performance compared to

individuals with MetS alone (Friedman et al., 2010; Li et al., 2014; Lindenmayer et al., 2012; Morgan et al., 2014; Nasrallah, 2010). This study reported herein can be thought of as an investigation of three main relationships: MetS and SMI, SMI and cognitive functioning, and MetS and cognitive functioning, with the goal of trying to understand the interplay of these three ideas in a young person with SMI.

2. Cognitive domains assessed in the MCCB

This chapter reviews commonly described cognitive domains, as referred to in the DSM-5 and MCCB, and also reviews the assessments in the MCCB. For each domain, a summary of what is included in terms of tasks, as well as appropriate neuroanatomical correlates are discussed.

Information Processing

Language processing is the set of activities having to do with communication and is often considered a fundamental area of cognition. It involves both auditory and visual aspects, including activities such as hearing, reading, speaking, writing, and comprehension.

Anatomically, the two main areas of interest are Broca's area and Wernicke's area (typically in the left cerebral hemisphere), which are responsible for speech production and language comprehension, respectively. There are neural pathways interconnecting these regions as well as to the occipital, sensory, and motor regions of the cortex. The left hemispheric processes also include some visual processing capabilities to support reading and object recognition (Corballis, 2003).

Visuospatial processing is the method by which information and comprehension are obtained from visual stimuli. One example of this is the construction of a three-dimensional experience when given the fact that the human eye captures two-dimensional data. Other examples may include the detection of similarities and differences between images and line orientation. Visuospatial processes appear to preferentially occur in the right cerebral hemisphere (Corballis et al., 1999, 2002).

Another aspect is that of processing speed - a measure of how fast a person can accommodate new information, understand it and make decisions. Processing speed is involved in all higher cognitive functions, including learning, memory, and executive skills, and is reflective of the interconnectivity between regions of the cortex. The natural course appears to be of processing speed declining with age, which may be a result of deteriorating neural structures and connections (white matter) and loss of grey matter volume, and may show regional specificity (Hong et al., 2015). Myelination supports improved processing speed as part of neural development, and this continues into adulthood (Chevalier et al., 2015; Magistro et al., 2015; O'Muircheartaigh et al., 2014).

Attention/Vigilance

Attention and vigilance can be summarised as the ability to focus on one stimulus while consciously attempting to ignore others. Different types of attention have been described including focused, sustained (or vigilance), selective, alternating, and divided (Cabeza and Nyberg, 2000). Focused attention relates to the ability to respond discretely to a specific stimulus. Sustained attention describes how one is able to maintain a consistent behavioural response during a continuous and repetitive activity. Selective attention is the ability to attend to one stimulus in the presence of distracting or competing stimuli. Alternating attention describes how an individual can shift attention between tasks requiring different cognitive requirements. Divided attention is the ability to respond simultaneously to multiple task demands; this is sometimes considered the highest level of attention. Uttal (2011) compiled a table of 46 components and types of attention described by various authors, demonstrating the variability of definitions used throughout the literature.

Attention can be a difficult quality to measure, as it is a very intrapersonal process, and inferences about one's attention abilities are often derived from behavioural results. Changes in attention, however, can occur without any noticeable external signs. The evaluation of attention can often overlap with evaluation of "working memory" and the interactions between the two can be quite complex (Awh et al., 2006). In 1890, William James stated that attention is necessary for consciousness, and "implies withdrawal from some things in order to deal effectively with others...," and is opposite to being "in the confused, dazed, scatterbrained state."(James, 1950)

In considering the neuroanatomy involved, one should consider two perspectives - a bottom up perspective starting with the sensory modality and associated structures, and a top down perspective that uses frontal lobe processes to inhibit and select stimulus monitoring. Greisbecht et al. (2006) examined the process by which visual attention seemed to proceed. They suggested, based on several works by Posner and various colleagues that the parietal lobe and temporoparietal junction were responsible for being able to disengage from one source, that the superior colliculus and related midbrain structures were responsible for the shifting, and that the thalamus was responsible for engaging the new stimulus (Posner et al., 1982; Posner et al., 1987; Posner et al., 1984). This speaks to the idea that this process may be better described through the idea of interacting neural networks such as described by Koziol et al. (2014). They describe two interacting networks (out of seven described in the article) with respect to attention - the dorsal attention network and the ventral attention network. The ventral attention network appears to be related to object salience, and the dorsal attention network related to the shifting functions. A third network, the frontoparietal network, includes

the dorsolateral prefrontal cortex, the anterior cingulate cortex, the anterior prefrontal cortex, the lateral cerebellum, the anterior insula, the caudate nucleus, and the inferior parietal lobe. This network has a role in both effortful focus and in automatic adjustments made outside of conscious awareness for both spatial and non-spatial attention (Corbetta et al., 2000; Hopfinger et al., 2000).

Working Memory

Working memory is where items from sensory memory can be held if attention is paid to them. It is often equated with "short-term" memory, although some will describe working memory as a special type of short-term memory. The duration of persistence is usually considered to be within the scale of minutes and generally consists of managing five to nine discrete items (Brown, 1964). Furthermore, it can be divided based on the type of information being stored, leading to verbal *vs.* non-verbal working memory. Maintenance of items in working memory requires sustained attention when the sensory stimulus is removed. While in this stage of memory, stored items can be manipulated, hence the term "working memory." These manipulations draw on processes from other domains such as reasoning and problem solving. It is likely that working memory is made up of several subsystems and not just short-term memory.

That working memory is not simply a single system is apparent when considering the neurological structures involved. Lesion studies have shown that temporal cortex lesions can lead to impairment in visual working memory (but not spatial working memory) and the opposite impairment with a parietal lesion (Owen et al., 1996; Pisella et al., 2004). Lateral

temporal lobe and temporoparietal lesions result in impaired verbal working memory, and correlate with findings from functional MRI studies (Binder and Desai, 2011; Crosson et al., 1999). As well, Crosson et al. (1999) suggested that there may be further anatomical separation based on whether the information is semantic, phonological or orthographic. It has also been shown that specific types of stimulus appear to correlate to specific structural regions (e.g. facial stimuli with the fusiform gyrus and scenes with the parahippocampus) (Ranganath et al., 2004). The regions involved may best be described as a network that involves the prefrontal cortex, temporal cortex and the parietal cortex with extensions into the somatosensory cortex and occipital cortex. Working memory also appears to have some lateralization in that the left ventral prefrontal cortex appears to be more involved with verbal tasks, and the right dorsal prefrontal cortex appears to have a role in spatial working memory tasks (Eriksson et al., 2015).

Learning and Memory

Learning and memory are two closely related concepts: "learning" can be described as the acquisition and encoding of new information and "memory" relates to the process by which this information is stored and retrieved. These domains can be further subdivided by content type (verbal *versus* visuospatial).

Memory can also be divided in a longitudinal sense: sensory, working/short-term (described above), and long-term. Sensory memory is a type of memory, originally described by George Sperling and termed by Ulric Neisser as "iconic memory," for a visual stimulus presented for a split second (Di Lollo, 1977). In Neisser's study, participants were flashed a grid of nine letters

and asked to recall one of the three rows immediately after. This demonstrated that the entire grid was held in memory for a short period of time. Similar experiments demonstrated a similar effect with sounds, which is referred to as "echoic memory" (Ardila et al., 1986; Gardiner, 1983; Kubovy and Howard, 1976). It has been postulated that the role of sensory memory is as a temporary holding stage until higher order memory processes can be applied (Huggins, 1975).

Long-term memory includes both recent and older facts, with older facts being more consolidated. Classically it consists of three phases: encoding, storing, and retrieving. Encoding is the process by which "meaning" is assigned to a concept, where other concepts can be used to index the idea being encoded. These other concepts are usually already resident in long-term memory and can be helpful to retrieve the concept being encoded. Storage is the consolidation of the memory, a step necessary to prevent loss of the memory. Consolidated memories are closely related to the idea of knowledge. The process of consolidation is affected by rapid-eye movement (REM) sleep, emotional states, and also by repetition and review (Squire, 2009). Retrieving memories is accomplished by the use of the indices and brings the concept into working memory where it can be manipulated.

Long-term memory can be subdivided into declarative and non-declarative memory. Declarative (or explicit) memory describes those memories that are related to events and facts and are usually available to consciousness. The details of these memories may have to do with biographical events (episodic), or simply words and ideas (semantic). Non-declarative (or implicit) memory includes procedural memories (i.e., skills such as riding a bicycle) and conditioned reflexes or emotions (Dubuc, 2002). These memories may not be available to

consciousness. It is possible to have deficits in one type of memory without the other type being affected (Okano et al., 2000).

The process of learning involves many neural circuits, beginning with sensory input (parietal and occipital regions), interpretation (frontal regions), the creation of associations (frontal temporal, and parietal regions), and finally the formation of the "memory." Traditionally, declarative memory (both semantic and episodic) appears to be most related to the hippocampus and other parts of the medial temporal lobe (Dubuc, 2002; Okano et al., 2000; Squire, 2009). Non-declarative memory appears to be integrated at various structural levels (reflex pathways, striatum, cerebellum, amygdala, and neocortex) although the hippocampus may play a role here as well, with respect to the initial consolidation of the memory (Dubuc, 2002; Okano et al., 2000; Squire, 2009).

Consolidation of memory occurs at two levels - a cellular level and a more "systems" level (involving synapses and circuits) (Dubuc, 2002). It appears to initially begin with hippocampal, striatal and cerebellar involvement when the episode occurs. The episode may then be consolidated during various phases of sleep involving the hippocampus, and is distributed over a number of cortical regions including the prefrontal cortex, the parietal cortex, and the neocortex (Dubuc, 2002; Squire, 2009). Consolidation may occur over a matter of days, with necessary repetitions (via neuronal reactivations in the relevant regions) taking place. At the cellular level, the neuron undergoes changes brought on by gene transcription and protein synthesis associated with the structural arrangement of the neuronal circuit and "transmission

efficacy of the synapse" (Dubuc, 2002; Okano et al., 2000). Over time, the role of the hippocampus appears to decline once the memory is consolidated (Squire, 2009).

Problem Solving and Reasoning

Problem solving and reasoning are processes that are part of a larger group of activities referred to as "executive functions" and are higher level cognitive skills. These processes are used to control and coordinate the above mentioned other cognitive processes, and may be subdivided into two domains: organizational and regulatory. Organizational processes include attention, planning, sequencing, problem solving, flexibility, and abstract thinking. Regulatory processes include both initiation and inhibition of behaviours and emotions. This type of activity also includes the monitoring of internal and external states, moral reasoning and decision making.

Studies involving individuals with brain injury have correlated executive dysfunction with the orbitofrontal cortex, prefrontal cortex, basal ganglia, and thalamus. The specific type of task appears to involve slightly different regions - for example, "object characteristic tasks" appeared to involve the whole brain (as measured by increased alpha activity), whereas a "name invention task" showed increased activity in the frontal lobes and decreased activity in the occipital lobe (Fink et al., 2009). Even within the prefrontal cortex, there appears to be some separation of function, with the dorsolateral prefrontal cortex being associated with the more cognitive aspects involved in executive functioning (including reasoning and problem solving) (Robinson et al., 2014). Other recent research appears to demonstrate that neural circuits appear to mediate the various executive processes. Stuss (2011) described several

relevant circuits including the lateral/medial/orbitofrontal circuit, associated with behavioural and emotional self-regulation, and a dorsolateral circuit, including the dorsolateral prefrontal cortex and connections to the caudate, associated with monitoring (right sided circuit) and task setting (left sided circuit). He also suggested that for each frontal cortical functional region, there was a corresponding basal ganglia area and a thalamic area - suggesting that there is some separation of these circuits.

Description of assessments within the MCCB

The MCCB is a standardised battery used to evaluate cognitive performance in adults with schizophrenia and was developed by the National Institute of Mental Health (NIMH) with participation from the Food and Drug Administration (FDA). The MCCB sub-tests were selected based on the following identified requirements: sensitive, having a short testing time, and suitable for retesting. The MCCB takes approximately 75-90 minutes to administer (Keefe et al., 2011). These qualities were identified as being relevant to help answer the question of whether or not pharmacological and/or cognitive interventions can improve cognitive outcome in individuals with schizophrenia. The following domains are measured with the MCCB: speed of processing (BACS: Symbol Coding, Category Fluency: Animal Naming, Trail Making Test: Part A); attention/vigilance (CPT-IP); working memory (WMS®-III: Spatial Span; Letter-Number Span); verbal learning (HVLT-R™); visual learning (BVMT-R™); reasoning and problem solving (NAB®: Mazes); and social cognition (MSCEIT™: Managing Emotions). The battery as a whole appears to be minimally affected by the clinical symptoms type (positive versus negative symptoms) and severity, but demonstrates a relatively high level of domain inter-correlation, suggesting the selected measures may not be “construct pure” (August et al., 2012). Green et

al. (2014) suggested that the battery continues to satisfy the design qualities and appears to be sensitive to showing improvements from interventions (including cognitive training), tracking with key biomarkers, and maintaining high test-retest reliability. Practice effects also appear to be minimal with this particular battery, in part due to a number of the assessments having multiple forms being available. This minimization of practice effects suggests that when changes are noted, that they can be attributed to other factors (Keefe et al., 2011; Roseberry and Kristian Hill, 2014).

The MCCB includes three tests sensitive to processing speed. From the Brief Assessment of Cognition in Schizophrenia (BACS) battery, the Symbol-Coding task requires the participant to place a corresponding digit below a nonsensical symbol using a reference key (Keefe, 1999). This task is timed, and is primarily a measure of processing speed. It is also influenced by working memory and attention, and can show some practice effects (Keefe et al., 2004). The Category Fluency: Animal naming task is a test where the participant is asked to name as many animals as they can within 1 minute. Although it is primarily a test of processing speed, performance on this task can be affected by language abilities and age (especially in geriatric populations) (Spreen, 1998). The Trail Making Test: Part A (TMT-A) (U.S. War Department, 1944) is a timed test where the participant is asked to draw a line between consecutively numbered circles that are placed randomly on a sheet. It is primarily a measure of processing speed, but is also influenced by mental flexibility, motor speed, and visual search and scanning skills (Tombaugh, 2004).

The MCCB also includes a computer-administered test of sustained attention denoted the Continuous Performance Test - Identical Pairs (CPT-IP) (Beck et al., 1956; Cornblatt et al., 1988). In this assessment, stimuli are flashed on the screen and the participant has to indicate if two successive stimuli are identical. Kahn et al. (2012) suggested that this assessment had good test-retest reliability, with mild practice effects. Furthermore, they also suggested that there were high correlations between this test of attention, and tasks of verbal memory, digit sequencing, and symbol coding from the BACS.

The MCCB tests of working memory include the Wechsler Memory Scale Spatial Span Test and the Letter-Number Sequencing Test (LNS) (WMS-III, Wechsler, 1997). The WMS-III Spatial Span is a measure of non-verbal working memory that uses a board having 10 irregularly spaced cubes. The participant has to tap the cubes in the same or reverse order as the assessor. It has been shown to be modestly correlated with visuospatial perception and processing speed, but does not appear to be entirely related to the LNS test (Wilde and Strauss, 2002). The LNS test is a measure of verbal working memory, in which the participant has to mentally reorder a string of letters and numbers and repeat it back to the assessor. This is an oral assessment. Performance on this test has been correlated with performance on the Continuous Performance Test, and assessments of verbal fluency, and reasoning (Murtagh et al., 2010).

The Hopkins Verbal Learning Test - Revised (HVLT-R) is an orally administered test in which a list of 12 words from three categories are presented, and the participant is instructed to recall as many words as possible after three learning trials (Brandt and Benedict, 2001). It is a test of verbal learning and memory, but correlated only weakly with general intelligence (Shapiro et

al., 1999). While similar to other tests of verbal learning, it has six alternate forms to reduce practice effects from repeated testing (Nuechterlein et al., 2008; Shapiro et al., 1999).

The assessment for visual learning is the Brief Visuospatial Memory Test – Revised (BVMT-R) (Benedict, 1997). In this assessment, the participant is shown an array of six figures for 10 seconds, and is then asked to reproduce as many of the figures as they can recall in their correct location on the answer sheet. This is repeated for a total of three trials. A fourth recall trial without presentation of the figures is administered approximately 25 minutes later as a measure of delayed recall. Similar to the HVLT-R above, the BVMT-R also has six alternate forms to reduce practice effects from repeated testing. In a group of older (aged 50 – 91 years) but otherwise healthy adults, it was observed that BVMT-R performance appeared to be predicted by a measure of processing speed, but not with a measure of executive function (Tam and Schmitter-Edgecombe, 2013).

The Neuropsychological Assessment Battery (NAB®): Mazes task serves as a measure of reasoning and problem solving, which are aspects of executive functioning (White and Stern, 2003). It consists of a series of 7 paper-and-pencil mazes of increasing difficulty. The solving of the mazes is timed and requires foresight and planning. There are 2 alternate forms available for this assessment to reduce practice effects from repeated testing. In comparison to other tests of executive functioning such as the Stroop test, and the Wisconsin Card Sorting Test, NAB®: Mazes was found to be comparable in terms of sensitivity in a small group of individuals with early-onset schizophrenia (age range 12 to 18 years), although the Stroop test was felt to be the most sensitive measure and authors also noted that the Wisconsin Card Sorting Test was

the more widely used of the three (Holmen et al., 2012). Unlike the other two, NAB®: Mazes appeared to key in on the planning role of executive functioning, and therefore caution may be required in interpreting results as it may be possible to have some preserved functioning in the other aspects – purposive action/inhibition, and effective purpose (Burgess et al., 1998; Scarpina and Tagini, 2017).

Lastly, the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT™): Managing Emotion is a paper-and-pencil multiple choice assessment that is meant to assess how individuals manage their own emotions, such as knowing how to calm oneself down when angry or upset (self-regulation), or to be able to empathize with and help another person regulate their emotions. This particular assessment was not used in the study described in Chapter 4.

This chapter is not meant to be an exhaustive exploration of each of these cognitive domains, but serves to allow one to appreciate the complexity in evaluating cognition and to understand the various factors that can affect it. Our understanding of cognition continues to evolve as we are better able to appreciate the intricacy of the human brain. The next chapter presents a review of the literature with respect to the following relationships: MetS and SMI, SMI and cognitive functioning, and MetS and cognitive functioning, with much of the focus on the latter. Chapter 4 is a study that analyzes the data available from an early psychosis intervention clinic with respect to MetS and cognitive functioning in this young population with SMI.

3. "Examining the relationships between metabolic syndrome, cognitive dysfunction, and severe mental illness - a literature review."

Manuscript Title

Examining the relationships between metabolic syndrome, cognitive dysfunction, and severe mental illness - a literature review.

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Abstract

There are many factors that contribute to the development of cognitive dysfunction. Dyslipidemia, hypo- and hyperglycemia, obesity, and hypertension are a few of the factors that are individually associated with cognitive dysfunction. Elements of these together also form the criteria for metabolic syndrome (MetS). MetS is present in about 24% of the general population, and its prevalence increases with age. It is directly associated with an increased risk of developing cardiovascular disease and diabetes, both of which in turn again impact cognitive function. The relevance of MetS to the psychiatric population has also been established, especially amongst those being treated with antipsychotic medications. However, more recent studies seem to indicate that simply having severe mental illness (SMI) may also put one at increased risk of developing MetS. Given this association, it is important to consider the cognitive impact on these individuals. Executive functioning, attention and memory have been implicated as affected areas of cognitive functioning, and are predominantly linked to the development of obesity and insulin resistance. Deficits in cognition affect the ability of the individual to maintain their own mental well-being. Individuals presenting with SMI are usually relatively young, and these complications are life-long, leading to increased mortality and morbidity. This article reviews the literature examining the relationships between metabolic syndrome, cognitive dysfunction, and severe mental illness.

Keywords: Cognition; metabolic syndrome; insulin resistance; obesity; severe mental disorders.

Introduction

Cardiovascular risk factors are one of the leading causes of mortality and morbidity in the general population, with ever increasing prevalence rates amongst adults. These risk factors include obesity, diabetes and insulin resistance, dyslipidemia, and hypertension, and together are often referred to as the metabolic syndrome (MetS) (Alberti et al., 2009). Analysis of data from the Canadian Health Measures Survey (CHMS) from 2007 to 2009 showed a prevalence of metabolic syndrome of 18.31% across all ages (Setayeshgar et al., 2012). Between 1998 and 2012, analysis of data from the National Health and Nutrition Examination Survey (NHANES) showed an overall increase in the prevalence of MetS amongst American adults, rising from 25.3% to 34.2% (Moore et al., 2017). Furthermore, the relative risk and resulting mortality and morbidity due to MetS appear to vary with demographic aspects such as age and gender. It may also not be surprising to find that MetS contributes to the increased mortality and morbidity in individuals with severe mental illness (SMI) (Toalson et al., 2004). These cardiovascular risk factors have also been associated with cognitive dysfunction in a number of populations including those with mental illness (Elias et al., 1997). Relatively few investigations, however, have examined potential relationships between these cardiovascular risk factors and changes in cognitive functioning in individuals with SMI. This paper is a literature review that discusses the relevant background and examines recent literature looking at the following three relationships: MetS and SMI, MetS and cognitive dysfunction, and SMI and cognitive dysfunction. Understanding these changes in cognitive functioning is important since early interventions for both SMI and MetS may improve long-term outcomes in terms of morbidity and mortality.

Metabolic Syndrome

Metabolic syndrome is a group of medical conditions that include obesity, lipid metabolism abnormalities, hypertension, and insulin resistance. Prevalence rates of MetS have been reported to be between 3.9% and 15.9% in populations of individuals presenting with early psychosis (De Hert et al., 2006; Mitchell et al., 2013; Papanastasiou, 2013; Vancampfort et al., 2013). Of note, the prevalence of MetS amongst adolescents in the Canadian general population has been reported as between 3.5% to 8% (Rao et al., 2014; Riediger and Clara, 2011; Setayeshgar et al., 2012). The variance in these ranges may be partly due to differences in the cut-off criteria for defining the presence of MetS (Table 1) proposed by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) (2002), and by the International Diabetes Foundation (IDF) (Alberti et al., 2005; Zimmet et al., 2007), with harmonised criteria being proposed in a joint statement (Alberti et al., 2009). The IDF also presented criteria for children and adolescents, stating that for those over 16 years of age, adult criteria should be used (Zimmet et al., 2007).

One thought is that the development of insulin resistance underlies all aspects of MetS (Alberti and Zimmet, 1998; Toalson et al., 2004), with another consideration being that central obesity leads to insulin resistance and the rest of MetS (Eckel et al., 2010). In recent pediatric studies, insulin resistance was also felt to be the main factor underlying obesity and MetS (Higgins and Adeli, 2017; Nelson and Bremer, 2010). In either case, it is suggested that insulin resistance promotes increased lipolysis, resulting in increased availability of free fatty acids. In the liver these fatty acids are synthesized into triglycerides and very low density lipoproteins. This in turn lowers high density lipoprotein levels. It is also postulated that insulin resistance results in

a decreased ability for vessels to dilate, resulting in elevated blood pressure. The connection between obesity and insulin resistance has been widely accepted, with previous evidence that weight loss often reduces insulin resistance. Methods of weight loss include dieting, the use of weight loss drugs, and bariatric surgery (Eckel et al., 2010; Grundy et al., 2005; Lavie et al., 2009).

Cognitive Domains of Relevance in Psychiatry

The concept of cognition has been a subject of interest for over 24 centuries, from the time of the early Greek philosophers to now. Over the years, great thinkers including Aristotle, Leonardo Da Vinci, John Locke, and Immanuel Kant have all described the idea of "cognition." In parallel, increased investigation of the human brain also took place. Thomas Willis (1621 – 1675) theorised that "higher" neurological structures were responsible for more complex processes, and the lower structures, which paralleled structures in lower animals, were responsible for more primitive processes such as reactions and autonomic functions. Through the 19th century, further work by individuals such as John Harlow, Pierre Paul Broca, Carl Wernicke, Korbinian Brodmann, William Beecher Scoville, and Santiago Ramon Y Cajal, often involving case reviews of patients with relatively discrete cerebral lesions such as Phineas Gage, Louis Victor Leborgne, and Henry Molaison, helped to localise function to specific regions and networks of neural circuits (Thiebaut de Schotten et al., 2015; Yuste, 2015).

Modern neuropsychology considers cognitive functioning as occurring within domains. Many of these domains can overlap, and also be further subdivided. DSM 5 (2013) proposed six key neurocognitive domains and a number of sub-domains (Figure 1).

A paradigm that is relevant to psychosis was defined as part of the development of the MATRICS Consensus Cognitive Battery (MCCB) and includes assessment in the domains shown in Figure 2 (Nuechterlein et al., 2004; Nuechterlein et al., 2008).

Like the domain of "Learning and Memory", the other domains can also be further divided into verbal and visuospatial/non-verbal sub-domains. This separation may be important to consider as it may correlate with lateralization of functioning (from a neuroanatomical perspective) (Caeyenberghs and Leemans, 2014; Nagel et al., 2013; Robinson et al., 2014; Thiebaut de Schotten et al., 2011).

Other domains to be considered in the cognitive evaluation of an individual would include areas such as motor speed and coordination, motivation, personality, and previous academic functioning or an estimated premorbid intelligence. These domains can influence the performance and the interpretation of the results from assessments designed to test cognitive functioning. It should also be noted that the various domains are often interrelated, i.e., deficits in one cognitive domain will likely impact performance in other domains (Keefe, 1995; Malik et al., 2017).

Methods

Articles to be included in this review were identified through a number of search strategies using the PubMed aka MEDLINE (PubMed version) database accessed online through the University of Alberta Libraries. The initial search strategy consisted of the following string of MeSH terms:

- ("Mental Disorders"[Mesh] AND "Metabolic Syndrome X"[Mesh]) AND ("Cognition"[Mesh] OR "Cognition Disorders"[Mesh])

When restricted to adolescents (13 – 18 years) and adults (19 – 44 years), 28 articles were returned of which 13 were found to be directly relevant to the topic after review of abstracts. The following searches were then carried out to retrieve articles that considered the three key relationships – MetS and Cognition, MetS and SMI, and SMI and Cognition:

- "Metabolic Syndrome X"[Mesh] AND ("Cognition"[Mesh] OR "Cognition Disorders"[Mesh])
- "Mental Disorders"[Mesh] AND "Metabolic Syndrome X"[Mesh]
- "Mental Disorders"[Mesh] AND ("Cognition"[Mesh] OR "Cognition Disorders"[Mesh])

To ensure a thorough review of the available online literature, further searches were conducted using other related keywords and keyphrases which included the following:

- Metabolic Syndrome X: MetS, Syndrome X, cardiovascular disease, obesity, diabetes, blood glucose, hypertension, dyslipidemia
- Cognition: cognitive dysfunction, neuropsychology, mental processes
- Mental Disorders: mental Illness, schizophrenia, psychotic disorders, bipolar disorder
- Antipsychotics including drug effects
- Substance use including cannabis
- Socioeconomic status

Articles were accessed through their online sources, and abstracts were reviewed for relevance of the article to this literature review. Further references were identified through review of the citations in each article and included where appropriate. Articles needed to be available in English, and there were no date restrictions. Research dealing with adolescents and younger adults as defined above were preferentially reviewed where possible.

Results and Discussion

Research looking at how various cardiovascular risk factors may contribute to the development of dementia has stimulated consideration of similar risk factors in the cognitive functioning of individuals with a psychotic illness (Friedman et al., 2010; Li et al., 2014; Lindenmayer et al., 2012; Morgan et al., 2014; Nasrallah, 2010). Individuals with psychosis and MetS, for example, have been reported to exhibit diminished cognitive functioning compared to those with psychosis without MetS. Previous studies relied predominantly on patients suffering from relatively longstanding psychosis, however, and the results are thus open to maturational factors such as illness progression or prolonged medication exposure that might cloud more direct attributions of the apparent negative association. There has been very little discussion about how these factors may play a role early in the course of illness (e.g., in first episode psychosis (FEP) patients). A recent study suggested that even in a relatively young group (mean age 30 years), a similar direct association between cognitive deficits and cardiovascular risk may be present (De Nijs and Pet, 2014); however, there was no discussion regarding the relationship between the particular factors of MetS and dysfunction in specific cognitive domains.

It is also unclear as to whether the cognitive changes are a result of developing these risk factors, or *vice versa*, or if there are other processes, such as oxidative stress and inflammation (Martinez-Cengotitabengoa et al., 2012), that contribute to both. C-reactive protein (CRP) is a traditional and reliable marker of systemic inflammation and has been noted to be elevated in those with schizophrenia, independent of medication use (Fernandes et al., 2016). Increased levels of CRP have also been associated with impaired cognitive performance (Johnsen et al., 2016). When considered along with the role of inflammation in the development of MetS, one can appreciate the potential role inflammatory processes play in the relationships between MetS, cognition, and mental illness. Inflammation and other potential factors involved in the relationship between these three phenomena can be appreciated in Figure 3. We now outline the topics of the three main relationships: SMI and MetS, cognitive dysfunction and SMI, and cognitive dysfunction and MetS (and its specific factors).

Severe Mental Illness and Metabolic Syndrome

It has been previously demonstrated that there is a significant association between MetS and SMI - due to both the use of antipsychotic medications and having SMI itself (American Diabetes Association, 2004; De Hert et al., 2006; Lorenz, 1922; Raphael and Parsons, 1921), with several mechanisms being postulated (De Hert et al., 2011; Dickinson and Harvey, 2009; Hasnain et al., 2010; Toalson et al., 2004).

The prevalence rates of MetS in those with SMI have been estimated in several trials. In the CATIE Schizophrenia trial, the overall prevalence of MetS was found to be 40.9% using NCEP-ATP III criteria (McEvoy et al., 2005). A Canadian study involving 240 subjects with

schizophrenia or schizoaffective disorder estimated a prevalence of 44.7% (Cohn et al., 2004). While ethnicity may play role in prevalence rates amongst the general population, it may not have the same moderating influence amongst individuals with SMI (Bressington et al., 2013). In a letter to the editor, Bartoli et al. (2013) suggest that prevalence rates for MetS amongst individuals with bipolar disorder was similar to those with schizophrenia, although a direct age-matched comparison of the pooled data was unfeasible, and hence, drawing a firm conclusion was not possible.

The connection between MetS and mental illness may at least partly reflect some shared aetiology between the two, mediated by inflammatory processes including cytokines and adipokines (Figure 4). For example, SMI or aspects of SMI have been associated with elevations in inflammatory markers such as TNF-α, CRP, and various inflammatory cytokines (Taylor et al., 2012). One suggested mechanism is that elevated circulating levels of adipokines and cytokines may directly and indirectly alter neuronal development and connectivity, resulting in mental illness (Castillo et al., 2016). Psychological and social factors may also play a role given the negative and neurovegetative symptoms that often accompany SMI, which may increase levels of inflammation. Many individuals with SMI are in lower socioeconomic classes, and are more likely to engage in unhealthy lifestyle choices and binge eating resulting in increased obesity and associated adipokine generation (McElroy, 2009). Additionally, studies have postulated a link between experiencing childhood trauma leading to developing both SMI and obesity. Childhood trauma is a known risk factor for obesity with one study showing a 1.4-1.6 fold increase in obesity and physical inactivity (Felitti et al., 1998; Gustafson and Sarwer, 2004; Palmisano et al., 2016). Many individuals with psychosis have a history of childhood trauma

(Roper et al., 2015) and also demonstrate a higher body mass index and CRP when compared to healthy controls (Hepgul et al., 2012). Furthermore, it is widely accepted that many psychotropic medications including antipsychotics are associated with significant weight gain, even as early as 6 weeks into treatment, with most weight gain within the first 6 months, which may exacerbate the above effects (Bak et al., 2014; Foley and Morley, 2011). Some of these connections described above may also be modulated via epigenetic mechanisms which provide one mechanism for the link between genetic factors and the effects of medication and other lifestyle factors (Hasnain et al., 2010; Shams and Muller, 2014).

Insulin resistance (whether resulting from having developed obesity or from other aetiology) has long been associated with schizophrenia and bipolar disorder prior to the availability of antipsychotic medication (Lorenz, 1922; Raphael and Parsons, 1921). A meta-analysis from 2016 suggests that Type 2 diabetes mellitus is associated with SMI with an increased relative risk over that of the general population (RR = 2.04, 95% CI: 1.69 – 2.49 for schizophrenia; RR = 1.89, 95% CI: 1.27 – 2.77 for bipolar disorder; and RR = 1.43, 95% CI: 0.88 – 2.25 for major depressive disorder, all compared to the general population), and more significant in multi-episode subjects than in single episode subjects when respectively compared to population controls. This appeared to be moderated in part by antipsychotic use. Subjects with SMI exhibit a higher prevalence of Type 2 diabetes when prescribed antipsychotic medication, and glucose regulation is negatively affected in a population of patients with schizophrenia and taking antipsychotics (Correll et al., 2015; Newcomer et al., 2002; Vancampfort et al., 2016). Diabetes and SMI may in fact have a bidirectional relationship, with the evolution of one disorder being affected by and affecting the other (Balhara, 2011; Popkin and Colon, 2001).

When these findings are taken along with the findings that connect obesity and SMI, it is clear that SMI and MetS are intimately related through a number of mechanisms from cellular/chemical processes through to psychosocial factors.

Cognitive Dysfunction in Severe Mental Illness

Cognitive dysfunction is an area of significant concern for individuals with SMI, both in active and stable phases (Corigliano et al., 2014; Keefe and Harvey, 2012; Nuechterlein and Dawson, 1984; Sponheim et al., 2010). Deficiencies in a range of domains including verbal memory, working memory, motor speed, attention, verbal fluency and executive functions have been noted (Altshuler et al., 2004; Gonzalez-Blanch et al., 2007; Keefe et al., 2004). Even at the time of first presentation, performance in the various cognitive domains appears to range from ~0.5 to ~3 standard deviations below the general population (Addington et al., 2003; Bilder et al., 2000; Fitzgerald et al., 2004), indicating that cognitive impairment may be part of the illness itself, and, moreover, this may worsen over time (Corigliano et al., 2014; Sponheim et al., 2010). This deficit also appears to be greater in individuals with schizophrenia when compared to others with SMI and other diagnoses such as mood disorders (Bora and Pantelis, 2015; Hill et al., 2004). This difference may reflect the relative level of disorganization that individuals with psychotic disorders experience compared to patients with other forms of mental illness.

The areas of dysfunction also appear to implicate changes in specific neuroanatomical regions. Minzenberg et al. (2009) reviewed 41 neuroimaging studies and found that individuals with schizophrenia showed reduced activation in the dorsolateral prefrontal cortex, the rostral/dorsal anterior cingulate cortex, the left thalamus, and inferior/posterior cortical area,

while having increased activity in several midline areas. They noted that there was modest variability depending on the specific task. Studies of individuals with first episode schizophrenia have shown reduced grey matter in the left superior temporal gyrus (Kasai et al., 2003; Kuroki et al., 2006), a region connected with working memory and language processing. Alterations in grey and white matter may not proceed equally in the various stages of psychosis and vary based on severity of symptoms (Pettersson-Yeo et al., 2013; Pettersson-Yeo et al., 2014). Grey matter deficits in the frontal, temporal, cingulate and insular cortex and thalamus have been described in individuals with schizophrenia, and decreased grey matter in the anterior cingulate and bilateral insula in individuals with bipolar disorder (Ellison-Wright and Bullmore, 2010). Such findings appear to correlate with the widespread cognitive dysfunction described above. This suggests that a disruption in appropriate neuroanatomical development in childhood and early adolescence may contribute to both the observed cognitive dysfunction and development of SMI.

Other Factors Affecting Cognitive Performance in SMI

The degree of cognitive impairment has been previously associated with the severity of negative symptoms and also with comorbid substance use (Addington et al., 2003; Fitzgerald et al., 2004; McCleery et al., 2006). These findings are not consistent, which may in part be due to differing methodologies and varying population characteristics (Potvin et al., 2008; Rund et al., 2004). Notably, several studies have reported that individuals with first-episode psychosis (FEP) using cannabis at the time of their presentation appeared to perform better on tests of visual memory, working memory, problem solving and executive functioning (Potvin et al., 2008), with most studies suggesting that cannabis users may have a higher level of premorbid functioning

(Cunha et al., 2013; Leeson et al., 2012; Rabin et al., 2011; Yucel et al., 2012). Not all studies appear to support these conclusions, with some studies finding no significant differences in overall cognitive performance (Bugra et al., 2013; Scholes and Martin-Iverson, 2010). Investigations of other substances including alcohol have produced even less consistent findings with respect to cognitive functioning (Donoghue et al., 2012; Pencer and Addington, 2003).

The use of pharmacotherapy has also been associated with mild to moderate benefits in cognitive functioning, even in the early phases of treatment (Davidson et al., 2009; Goldberg et al., 2007; Hill et al., 2010; Purdon et al., 2000; Sumiyoshi, 2008). Furthermore, the duration of untreated illness and of untreated psychosis appear to have little if any relationship to the degree of cognitive impairment in FEP patients (Lutgens et al., 2014; Rapp et al., 2013; Rund et al., 2004). The mechanism by which pharmacotherapy may affect cognitive functioning is not entirely clear, i.e. whether it is the result of symptom reduction, improvement in motivation for cognitive assessment, or some other methodological factor such as the learning that can be associated with repeated testing. Weickert et al. (2003) did attempt to address this question with a small sample of patients using an interesting method where one group was first assessed while on medication and then after a washout and starting placebo, and the other group was assessed in the opposite direction. They found that in both groups, individuals did perform better on cognitive assessments when on medication ($p < 0.04$) compared to when on placebo; the medication effect did not, however, appear to be mediated by symptom severity as indicated by the total PANSS score.

It has also been noted that the specific medication may not play a significant role in the early phases, with no between group differences noted on in a study by Gonzalez-Blanch et al. (2008) looking at differences between risperidone, olanzapine, and haloperidol over an initial 6 week period of treatment in an FEP clinic. Furthermore, over a two year period, a prior 2002 study did not find any significant relative benefit of risperidone in comparison to haloperidol (Green et al., 2002). This is in contrast to another study which appeared to suggest that treatment with risperidone provided greater cognitive benefits than treatment with haloperidol over a 3-month period (Harvey et al., 2005). In all cases, there was noted to be a performance improvement over time for all the medication groups; the noted differences between the studies may be related to dosing, specific time frame of assessment and/or the relative baseline characteristics of the populations in the respective studies.

Other demographic factors such as age, gender, years of education, socio-economic status, and occupational status have also been associated with cognitive performance (Elias et al., 1997; Farmer et al., 1995; Kaplan et al., 2001), although the direction of effect is not always clear. For example, in studies of individuals with psychosis, active employment may result from improved cognitive functioning, and continued improvements in cognitive functioning may result from being engaged in work or school (Dickerson et al., 2007; McGurk and Mueser, 2004). This suggests that these factors should be considered as possible confounders when looking at relationships involving cognition.

Cognitive Dysfunction and Metabolic Syndrome

Studies examining the link between cognitive dysfunction and features of the MetS have mainly focused on middle aged to older members of the general population, and often in the context of developing dementia as a result of cardiovascular disease (Yates et al., 2012). Several studies involving non-geriatric general populations revealed that memory, executive functioning, processing speed, and general intellect were related to symptoms of MetS, with preliminary results implicating cognitive domain specific effects (Elias et al., 2005; Gatto et al., 2008; Hassenstab et al., 2010; Pavlik et al., 2005; Segura et al., 2009; Taylor and MacQueen, 2007; Tournoy et al., 2010; Troisi, 2009; van den Berg et al., 2009; Vieira et al., 2011). The predominant emphasis of these studies was the role of glucose dysregulation and obesity on cognition, with a minor emphasis on roles of dyslipidemia and hypertension, and so the focus here will also remain on the relationships with glucose dysregulation and obesity.

Obesity

Obesity is a growing concern amongst the general population, and has been shown to affect cognitive functioning (Crichton et al., 2012; Elias et al., 2003). Obesity has been associated with an increased risk of dementia, with a proposed mechanism being that adiposity promotes a sub-clinical state of inflammation, which has a deleterious effect on neuronal functioning that may contribute to cognitive decline and possibly dementia (Taylor and MacQueen, 2007). Animal and human studies (Farr et al., 2008; Lavie et al., 2009) have implicated direct and indirect contributions of obesity to glucose dysregulation and dyslipidemia that may also be relevant to cognitive dysfunction.

The direct evidence for obesity affecting specific cognitive domains is mixed. A review by van den Berg et al. (2009) noted that obesity was mostly associated with impairments in cognitive flexibility, as well as perception and construction. In a relatively youthful (i.e., non-geriatric) Canadian First Nations population (median age 39 years; range 19 to 65 years), obesity, measured as either increased BMI or increased waist circumference, was related to diminished executive functioning, measured by the Trail Making Test - Parts A and B (Fergenbaum et al., 2009). Gunstad et al. (2006) reported that increased BMI negatively affected verbal memory across the adult lifespan. In contrast, a subsequent study did not find any association between obesity and verbal memory, but reported negative associations between obesity (measured as waist-to-hip ratio) and both executive and visuomotor skills, and noted possible gender-specific effects (Wolf et al., 2007). From the Framingham heart study, obesity appeared to affect visual working memory and global cognitive functioning, but in men only (Elias et al., 2005).

A number of studies noted that obesity did not appear to diminish cognitive functioning directly and at least one study suggested some protective effects of obesity. In the more elderly, obesity appeared to even reduce the risk of developing dementia. As well, no association was observed between obesity and cognitive status after adjusting for age and socioeconomic status (SES). It has been suggested that low SES is a strong positive correlate of obesity, with lower SES being associated with decreased intake of fruits and vegetables, and increased intake of foods high in fats (Taylor and MacQueen, 2007). Since low SES also appears to be correlated with poorer school performance, overall cognitive achievement, and impaired neurological development, a low SES may provide an additional explanation linking obesity and cognitive dysfunction (Hair et al., 2015; Noble et al., 2005).

In children and adolescents, a review by Liang et al. (2014) concluded that obesity had similar effects in children and adolescents, affecting executive functioning, attention, visuospatial performance and motor skills. In contrast, a study involving 478 children and adolescents did not find an association between increased BMI and cognitive functioning (executive functioning, attention, verbal memory, language, and motor skills) (Gunstad et al., 2008). The same study noted that underweight females performed more poorly on a test of verbal recall. In examining brain abnormalities, Yau et al. (2012) reported that obese nondiabetic adolescents (otherwise meeting criteria for MetS) had reduced hippocampal volumes and compromised white matter microsctructural integrity, along with lower scores on cognitive measures (impaired attention and mental flexibility and poorer academic performance) when compared to a control group of individuals who were not obese and did not meet criteria for MetS. They suggested that obesity may represent a prediabetic stage (where serum glucose levels are > 6.1 mmol/l and < 7.0 mmol/l), with further impairment resulting from developing compromised glucose regulation. A review by Yates et al. (2012) noted that most studies of children and adolescents have reported lower cognitive skills associated with obesity, but there was no remarkable cognitive-domain specificity to the association aside from preliminary speculation of greater limitations of attention and executive functions. The authors make note of the relative paucity of investigations with children and adolescent samples, as well as the significant variation in assessment methodology and management of relevant covariates.

Dysglycemia

van den Berg et al. (2009) noted that having Type 2 diabetes was associated with impairments in processing speed and attention. Results were mixed, however, for patients exhibiting

impaired glucose tolerance (IGT) (fasting glucose level < 7.0 mmol/l and 2hr-glucose level ≥7.8 and <11.1 mmol/l), with a another review suggesting a direct association between IGT and memory impairment compared to controls, along with impairment in attention and psychomotor functioning; they also noted a number of studies that detected only small effect sizes which were not statistically significant (Lamport et al., 2009). Gluck et al. (2013) reported that even mildly elevated fasting blood glucose levels in the non-diabetic range, but reflecting the presence of IGT, were associated with lower scores on the Stroop Color Word task, suggesting a detrimental effect of glucose elevations on one test of executive skills related to suppression of lexical interference.

Although relatively few studies have examined associations between non-diabetic range fasting blood glucose and cognitive skills, several investigations have examined random blood glucose levels and cognitive performance in healthy adults, with results suggesting potential cognitive benefits from higher values within the normal range (Meikle et al., 2004; Smith et al., 2011). Earlier studies of individuals with schizophrenia noted that ingestion of glucose prior to a cognitive assessment appeared to improve recognition, verbal episodic and spatial memory (Fucetola et al., 1999; Newcomer et al., 1999). The investigation undertaken by Meikle et al. (2004) included a glucose loading manipulation that entailed consumption of a drink containing a placebo, 25g of glucose, or 50g of glucose. On a visual recognition memory search task for letters presented on a computer screen, glucose loading benefited an older subgroup of this sample (mean age 38.4 years, SD=6.7 years), but not a younger subgroup (mean age 21.8 years, SD=3.3 years), and only under relatively high cognitive load demands. Glucose elevations may thus facilitate some aspects of cognition when an individual may be presumed to have

experienced age-related decline from a previous higher level of function. In the same study, a test of delayed verbal recall also demonstrated a benefit of glucose loading, but some improvement was apparent in both age groups. This glucose supplement study also introduced a 'glucose recovery index' (i.e., classification as good or poor regulators as higher or lower than the median difference between pre- and post-loading blood glucose levels, respectively), but they did not observe reliable effects of regulation on cognitive test performance.

A more recent investigation of relatively young adults (mean age 20 years; range 18 to 30 years) reported beneficial effects of a glucose supplement in individuals with poorer glucose regulation, with a 25g dose resulting in gains relative to placebo on tests of working memory (i.e., serial 7s, Corsi block task, immediate verbal recall, delayed verbal recall, and speed of word recognition), and significant gains from 60g on tests of working memory (i.e., serial 3s, Corsi block task, and speed of word recognition) (Owen et al., 2012). Noteworthy may be the lack of significant improvement from 60g ingestion on tests with more significant cognitive load (i.e., serial 7s, immediate verbal recall, delayed verbal recall). A subsequent investigation by the same group suggested that a 25g glucose load may preferentially benefit individuals with poorer glucoregulation when compared to those with better regulation on the more challenging tasks involving recall performance (Owen et al., 2013). This may be relevant because the earlier study noted a similar downward trend towards an upside-down U-shaped dose-response curve in their younger subgroup on a visual search task (Meikle et al., 2004).

The mechanism by which glucose dysregulation affects cognitive performance appears to be multifactorial. One line of investigation considers that glucose regulation appears to be

associated with glucocorticoid activity, cholesterol deposition, and alterations in neuronal activity possibly mediated by idiosyncratic myelin formation and altered signal transduction (Taylor and MacQueen, 2007). The hippocampus has a high co-localisation of both cortisol and insulin receptors, so it is reasonable to hypothesize that hippocampal function, and therefore memory, is affected by both cortisol and insulin activity. Previous animal studies have demonstrated that increased glucocorticoid levels inhibit the transportation of glucose into hippocampal neurons and in humans, an injection of cortisol can affect memory (Convit, 2005). Owen et al. (2013) offered speculation of a potential role for cortisol where cortisol response to stressors is blunted by the administration of glucose. Individuals whose cognitive functioning appeared to respond to glucose administration also had a greater cortisol response to stress.

Glucose dysregulation is also associated with other endocrine dysfunctions that can contribute independently and interdependently to MetS and cognitive dysfunction. For example, in animal studies, leptin resistance has been considered to be a component of diabetes, but also appears to have a direct role in the process of learning and memory (Harvey, 2007). And on a background of insulin resistance being associated with chronic inflammation, Mortby et al. (2013) proposes that that this linkage may account for the neurodegenerative changes associated with even only high normal (< 6.1 mmol/L) blood glucose levels in their study population.

MetS in Younger Individuals

With respect to studies involving younger individuals, Yau et al. (2012) was one of the first groups to report a relationship between cognitive functioning and MetS in a younger

population, with young individuals having MetS exhibiting diminished attention, mental flexibility, and academic achievement. They also noted that cognitive performance was inversely associated with the number of MetS criteria met, suggesting that there may be a compounding effect with each additional MetS factor. It should be noted that in this study, both samples performed within the normal range on the various cognitive measures. Other studies involving young individuals have examined the relationship between cognitive functioning and diabetes, obesity, or hypertension (but not MetS) - where cognitive dysfunction represents a symptom of end organ damage with the end organ of consideration being the brain (Gunstad et al., 2006; Gunstad et al., 2008; Lande and Kupferman, 2015; Messier et al., 2011; Naguib et al., 2009; Ohmann et al., 2010; Yates et al., 2012). Again, it is difficult to draw specific conclusions, given the variation of cognitive domains and metabolic factors being assessed, and the specific assessments being used.

Strengths and Limitations in the Literature

In general, it is important to note that the various factors making up MetS may have differential effects, affecting different cognitive domains. There are a large number of studies that have looked at the relationships between MetS and cognitive functioning, especially in older individuals and in the general populations, such as in the Framingham Study. More recent awareness of MetS in the adolescent and young adult population has also generated an interest in examining the relationships between MetS and cognitive functioning in this population. Drawing on the conclusions in this literature allows for one to start generating predictive models to be applied to other more specific populations, such as those being treated for FEP.

There are some limitations to note as well. One issue is a lack of consensus on the most appropriate cognitive domains to assess, and a lack of consensus on the most useful instruments to assess each relevant domain. In many studies, no premorbid estimates of intellect are made, making within subject comparisons more difficult to assess. Study design (cross-sectional *versus* longitudinal) and the specific population evaluated (in terms of gender, age group and education) are also not consistent, making it difficult to draw firm conclusions about some of the relationships with cognition. Nonetheless, the consideration of cognitive impairment being a sign of organic neuropathology parallels findings in the elderly, where cardiovascular pathology has been associated with dementia (Crichton et al., 2012; Harrison et al., 2014; Panza et al., 2010). As well, there are few studies to date looking at the above relationships with respect to children, adolescents, or young adults.

Conclusions

This review of the literature continues to support the suggestion that developing MetS is associated with a worsening of cognitive performance, with obesity correlating with impairments primarily in executive functioning and memory, and dysglycemia with that of processing speed and memory. When including the additional factor of SMI, individuals appear to suffer a greater burden of cognitive dysfunction. This suggests that there may be similar mechanisms at work relating cognitive dysfunction and MetS in patients with SMI.

The interplay of the three phenomena warrants clinical attention. It may well be that several underlying mechanisms, touched upon in this review, connect SMI, MetS, and cognitive dysfunction. The interactions may occur on several levels, from genetic and cellular

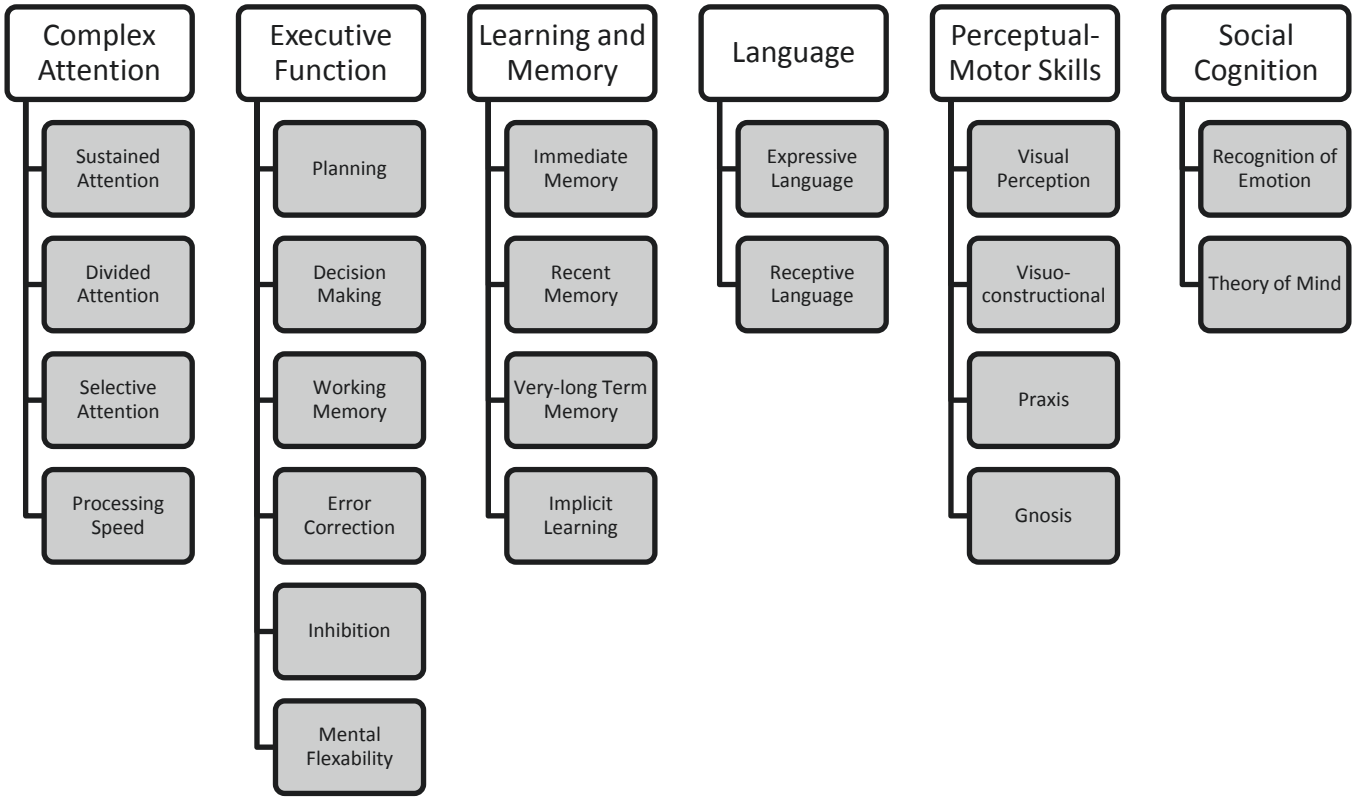
mechanisms to psychological and social ones. Understanding these interactions could facilitate better clinical care including specific preventative measures and targeted clinical interventions. This is especially relevant to individuals experiencing their first episode of psychosis, as cognitive impairment can affect patients' ability to actively engage in and be partners in their own care and treatment. Early, appropriate and effective interventions for both the psychiatric and medical symptoms can lead to better outcomes for this population; we recommend further research on the relationships outlined above for young people with SMI.

Table 1: **Criteria for MetS as proposed by IDF, NCEP-ATP III, and Harmonised criteria**

Criteria*	IDF	NCEP-ATP III	Harmonised
Obesity (measured by waist circumference)	≥ 94 cm for Europid men, ≥ 90 cm for non-Europid men, ≥ 80 cm for women	> 102 cm for men, > 88 cm for women	≥ 94 cm for Europid men, ≥ 90 cm for non-Europid men, ≥ 80 cm for women
Elevated Trigylcerides	≥ 1.7 mmol/L or on specific treatment	≥ 1.69 mmol/L	≥ 1.7 mmol/L or on specific treatment
Low HDL	< 1.03 mmol/L for men, < 1.29 mmol/L for women, or on specific treatment	< 1.03 mmol/L for men, < 1.29 mmol/L for women	< 1.0 mmol/L for men, < 1.3 mmol/L for women, or on specific treatment
Elevated Blood Pressure	Systolic BP ≥ 130 mm Hg, Diastolic BP ≥ 85 mm Hg, or previously diagnosed HTN	BP ≥ 130/85 mm Hg	Systolic BP ≥ 130 mm Hg, Diastolic BP ≥ 85 mm Hg, or previously diagnosed HTN
Elevated Fasting Plasma Glucose	≥ 5.6 mmol/L, or previously diagnosed Type 2 diabetes	≥ 6.1 mmol/L	≥ 5.6 mmol/L, or previously diagnosed Type 2 diabetes

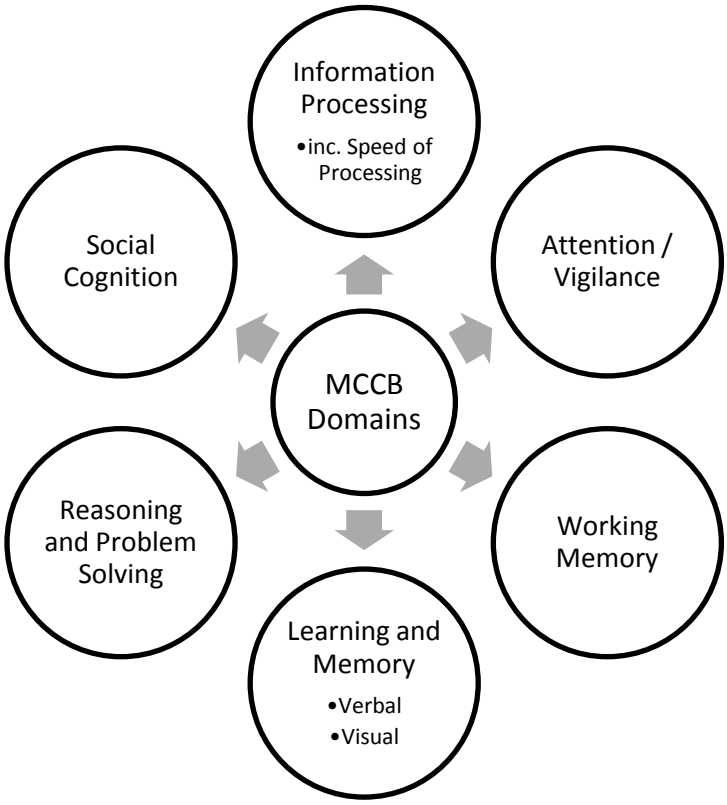
*Under the IDF definition, obesity plus any 2 of the remaining 4 criteria must be met for a diagnosis for MetS, while under NCEP-ATP III definition, 3 of out of 5 criteria must be met for the diagnosis. Under the Harmonised criteria (having the same cut-offs as the IDF criteria), meeting any 3 out of the 5 criteria would qualify for a diagnosis of MetS. Contents adapted from respective guidelines proposed by NCEP-ATP III (2002), IDF (Alberti et al., 2005; Zimmet et al., 2007), and harmonised criteria being proposed in a joint statement (Alberti et al., 2009).

Figure1: Neurocognitive domains as defined in DSM 5.*



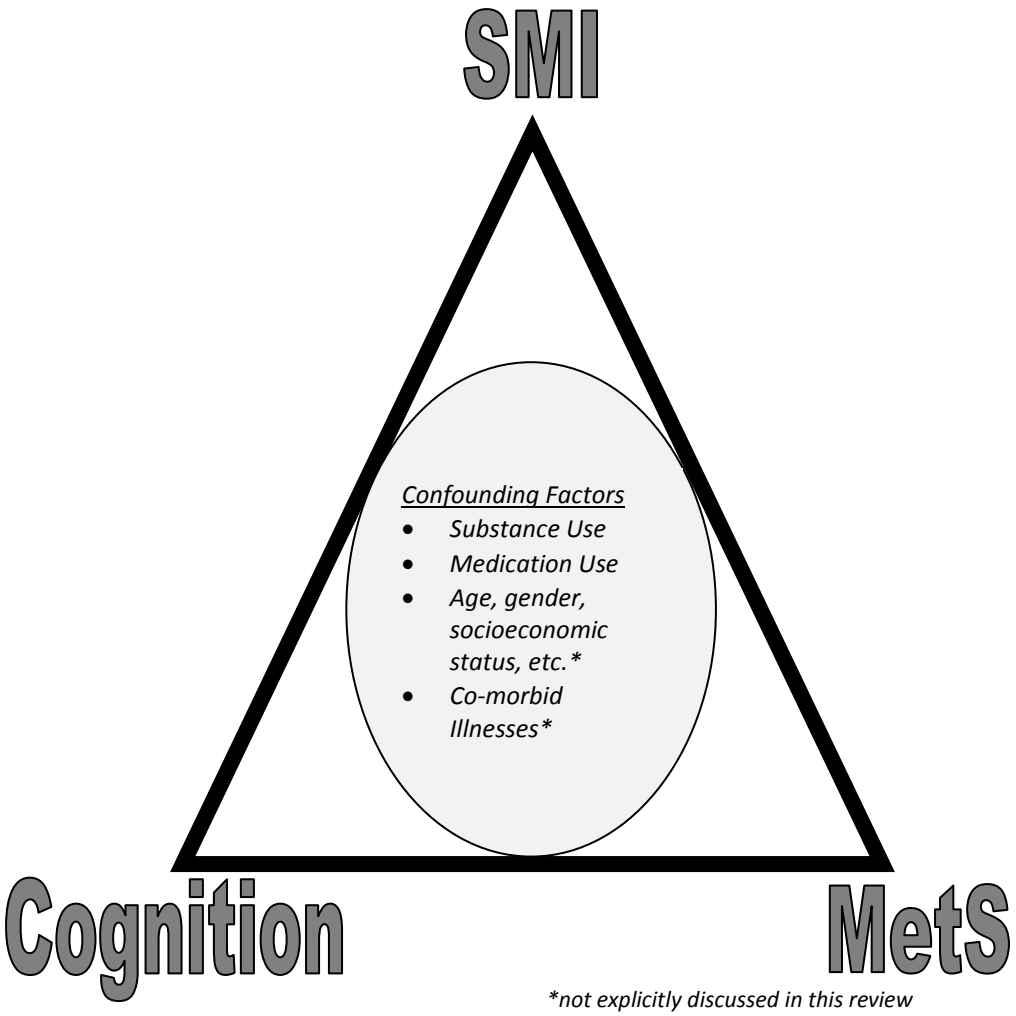
*Content adapted from the "Neurocognitive Disorders" chapter in DSM 5 (2013)

Figure 2: Domains Assessed by the MCCB.



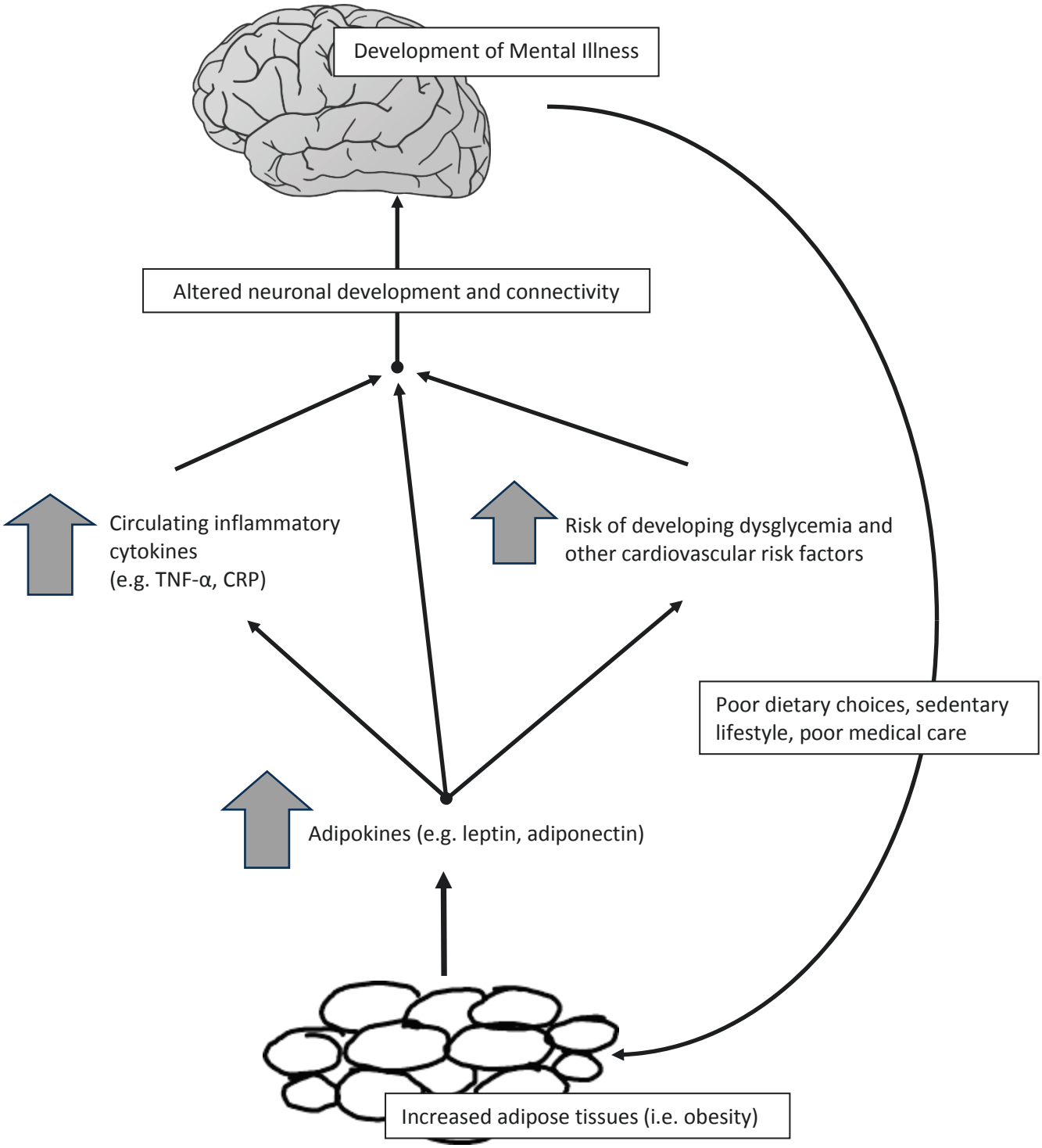
*content adapted from www.matricsinc.org/mccb/ (accessed February 2016)

Figure 3: Relationships between SMI, MetS, and Cognition and confounding factors of consideration.



*not explicitly discussed in this review

Figure 4: One possible mechanism showing linkages between increased adipose tissue from the development of obesity, leading to increased levels of adipokines and cytokines, and developing mental illness.



Acknowledgements

We would like to acknowledge the support of the University of Alberta Department of Psychology Industrial Internship Program.

Contributions:

Dr. Sudhakar Sivapalan was primarily responsible for the searching and reviewing of the literature for inclusion in this review. Dr. Sivapalan was also the primary author of the manuscript. Dr. Katherine Aitchison and Dr. Scot Purdon provided guidance for the review process and significant feedback and review of the manuscript. All the authors have reviewed and approved the final manuscript.

Funding

Dr. Sivapalan received support from the University of Alberta, Department of Psychiatry to conduct a M.Sc. in Psychiatry at the University of Alberta, and from Alberta Health Services as a Resident Physician. Dr. Aitchison holds an Alberta Centennial Addiction and Mental Health Research Chair, funded by the Government of Alberta. Dr. Purdon is supported by Alberta Health Services Addictions and Mental Health – Edmonton Zone. Funding for this study was provided, in part, by the University of Alberta Bebensee Schizophrenia Research Unit.

References

2002. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 106(25), 3143-3421.

2013. Diagnostic and statistical manual of mental disorders : DSM-5, 5th ed. ed. American Psychiatric Publishing, Washington, D.C.

Addington, J., Brooks, B.L., Addington, D., 2003. Cognitive functioning in first episode psychosis: initial presentation. Schizophr. Res. 62(1-2), 59-64.

Alberti, K.G., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., Fruchart, J.C., James, W.P., Loria, C.M., Smith, S.C., Jr., International Diabetes Federation Task Force on, E., Prevention, Hational Heart, L., Blood, I., American Heart, A., World Heart, F., International Atherosclerosis, S., International Association for the Study of, O., 2009. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 120(16), 1640-1645.

Alberti, K.G., Zimmet, P., Shaw, J., 2005. The metabolic syndrome--a new worldwide definition. Lancet. 366(9491), 1059-1062.

Alberti, K.G., Zimmet, P.Z., 1998. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabetic Med. 15(7), 539-553.

Altshuler, L.L., Ventura, J., van Gorp, W.G., Green, M.F., Theberge, D.C., Mintz, J., 2004. Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. Biol. Psychiat. 56(8), 560-569.

American Diabetes Association, 2004. Consensus development conference on antipsychotic drugs and obesity and diabetes. J. Clin. Psychiatry. 65(2), 267-272.

Bak, M., Fransen, A., Janssen, J., van Os, J., Drukker, M., 2014. Almost all antipsychotics result in weight gain: a meta-analysis. PLOS ONE. 9(4), e94112.

Balhara, Y.P.S., 2011. Diabetes and psychiatric disorders. Indian. J. Endocr. Metab. 15(4), 274-283.

Bartoli, F., Carra, G., Crocamo, C., Carretta, D., Clerici, M., 2013. Bipolar disorder, schizophrenia, and metabolic syndrome. Am. J. Psychiatry. 170(8), 927-928.

Bilder, R.M., Goldman, R.S., Robinson, D., Reiter, G., Bell, L., Bates, J.A., Pappadopulos, E., Willson, D.F., Alvir, J.M., Woerner, M.G., Geisler, S., Kane, J.M., Lieberman, J.A., 2000. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. Am. J. Psychiatry. 157(4), 549-559.

Bora, E., Pantelis, C., 2015. Meta-analysis of Cognitive Impairment in First-Episode Bipolar Disorder: Comparison With First-Episode Schizophrenia and Healthy Controls. Schizophr. Bull. 41(5), 1095-1104.

Bressington, D.T., Mui, J., Cheung, E.F., Petch, J., Clark, A.B., Gray, R., 2013. The prevalence of metabolic syndrome amongst patients with severe mental illness in the community in Hong Kong--a cross sectional study. BMC Psychiatry. 13, 87.

Bugra, H., Studerus, E., Rapp, C., Tamagni, C., Aston, J., Borgwardt, S., Riecher-Rossler, A., 2013. Cannabis use and cognitive functions in at-risk mental state and first episode psychosis. Psychopharmacology (Berl). 230(2), 299-308.

Caeyenberghs, K., Leemans, A., 2014. Hemispheric lateralization of topological organization in structural brain networks. Hum. Brain Mapp. 35(9), 4944-4957.

Castillo, R.I., Rojo, L.E., Henriquez-Henriquez, M., Silva, H., Maturana, A., Villar, M.J., Fuentes, M., Gaspar, P.A., 2016. From Molecules to the Clinic: Linking Schizophrenia and Metabolic Syndrome through Sphingolipids Metabolism. Front. Neurosci-Switz. 10, 488.

Cohn, T., Prud'homme, D., Streiner, D., Kameh, H., Remington, G., 2004. Characterizing coronary heart disease risk in chronic schizophrenia: high prevalence of the metabolic syndrome. Can. J. Psychiatry. 49(11), 753-760.

Convit, A., 2005. Links between cognitive impairment in insulin resistance: an explanatory model. Neurobiol. Aging. 26 Suppl 1, 31-35.

Corigliano, V., De Carolis, A., Trovini, G., Dehning, J., Di Pietro, S., Curto, M., Donato, N., De Pisa, E., Girardi, P., Comparelli, A., 2014. Neurocognition in schizophrenia: from prodrome to multi-episode illness. Psychiat. Res. 220(1-2), 129-134.

Correll, C.U., Detraux, J., De Lepeleire, J., De Hert, M., 2015. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry. 14(2), 119-136.

Crichton, G.E., Elias, M.F., Buckley, J.D., Murphy, K.J., Bryan, J., Frisardi, V., 2012. Metabolic syndrome, cognitive performance, and dementia. J. Alzheimers Dis. 30 Suppl 2, S77-87.

Cunha, P.J., Rosa, P.G., Ayres Ade, M., Duran, F.L., Santos, L.C., Scazufca, M., Menezes, P.R., dos Santos, B., Murray, R.M., Crippa, J.A., Busatto, G.F., Schaufelberger, M.S., 2013. Cannabis use, cognition and brain structure in first-episode psychosis. Schizophr. Res. 147(2-3), 209-215.

Davidson, M., Galderisi, S., Weiser, M., Werbeloff, N., Fleischhacker, W.W., Keefe, R.S., Boter, H., Keet, I.P., Prelipceanu, D., Rybakowski, J.K., Libiger, J., Hummer, M., Dollfus, S., Lopez-Ibor, J.J., Hranov, L.G., Gaebel, W., Peuskens, J., Lindefors, N., Riecher-Rossler, A., Kahn, R.S., 2009. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). Am. J. Psychiatry. 166(6), 675-682.

De Hert , M., Correll, C.U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Gautam, S., Moller, H.J., Ndetei, D.M., Newcomer, J.W., Uwakwe, R., Leucht, S., 2011. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry. 10(1), 52-77.

De Hert, M., van Winkel, R., Van Eyck, D., Hanssens, L., Wampers, M., Scheen, A., Peuskens, J., 2006. Prevalence of diabetes, metabolic syndrome and metabolic abnormalities in schizophrenia over the course of the illness: a cross-sectional study. Clin. Pract. Epidemiol. Ment. Health. 2, 14.

De Nijs, J., Pet, M.A., 2014. Metabolic syndrome in patients with schizophrenia is associated with poor cognitive performance and poor premorbid school performance. Eur. Neuropsychopharm. 24, S485-S486.

Dickerson, F.B., Stallings, C., Origoni, A., Boronow, J.J., Sullens, A., Yolken, R., 2007. The association between cognitive functioning and occupational status in persons with a recent onset of psychosis. J. Nerv. Ment. Dis. 195(7), 566-571.

Dickinson, D., Harvey, P.D., 2009. Systemic hypotheses for generalized cognitive deficits in schizophrenia: a new take on an old problem. Schizophr. Bull. 35(2), 403-414.

Donoghue, K., Mazzoncini, R., Hart, J., Zanelli, J., Morgan, C., Dazzan, P., Morgan, K.D., Murray, R.M., Jones, P.B., Doody, G.A., 2012. The differential effect of illicit drug use on cognitive function in first-episode psychosis and healthy controls. Acta. Psychiatr. Scand. 125(5), 400-411.

Eckel, R.H., Alberti, K.G., Grundy, S.M., Zimmet, P.Z., 2010. The metabolic syndrome. Lancet. 375(9710), 181-183.

Elias, M.F., Elias, P.K., Sullivan, L.M., Wolf, P.A., D'Agostino, R.B., 2003. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. Int. J. Obes. Relat. Metab. Disord. 27(2), 260-268.

Elias, M.F., Elias, P.K., Sullivan, L.M., Wolf, P.A., D'Agostino, R.B., 2005. Obesity, diabetes and cognitive deficit: The Framingham Heart Study. Neurobiol. Aging. 26 Suppl 1, 11-16.

Elias, P.K., Elias, M.F., D'Agostino, R.B., Cupples, L.A., Wilson, P.W., Silbershatz, H., Wolf, P.A., 1997. NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. Diabetes Care. 20(9), 1388-1395.

Ellison-Wright, I., Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr. Res. 117(1), 1-12.

Farmer, M.E., Kittner, S.J., Rae, D.S., Bartko, J.J., Regier, D.A., 1995. Education and change in cognitive function. The Epidemiologic Catchment Area Study. Ann. Epidemiol. 5(1), 1-7.

Farr, S.A., Yamada, K.A., Butterfield, D.A., Abdul, H.M., Xu, L., Miller, N.E., Banks, W.A., Morley, J.E., 2008. Obesity and hypertriglyceridemia produce cognitive impairment. Endocrinology. 149(5), 2628-2636.

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., Koss, M.P., Marks, J.S., 1998. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am. J. Prev. Med. 14(4), 245-258.

Fergenbaum, J.H., Bruce, S., Lou, W., Hanley, A.J., Greenwood, C., Young, T.K., 2009. Obesity and lowered cognitive performance in a Canadian First Nations population. Obesity (Silver Spring). 17(10), 1957-1963.

Fernandes, B.S., Steiner, J., Bernstein, H.G., Dodd, S., Pasco, J.A., Dean, O.M., Nardin, P., Goncalves, C.A., Berk, M., 2016. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol. Psychiatry. 21(4), 554-564.

Fitzgerald, D., Lucas, S., Redoblado, M.A., Winter, V., Brennan, J., Anderson, J., Harris, A., 2004. Cognitive functioning in young people with first episode psychosis: relationship to diagnosis and clinical characteristics. Aust. N. Z. J. Psychiatry. 38(7), 501-510.

Foley, D.L., Morley, K.I., 2011. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. Arch. Gen. Psychiat. 68(6), 609-616.

Friedman, J.I., Wallenstein, S., Moshier, E., Parrella, M., White, L., Bowler, S., Gottlieb, S., Harvey, P.D., McGinn, T.G., Flanagan, L., Davis, K.L., 2010. The effects of hypertension and body mass index on cognition in schizophrenia. Am. J. Psychiatry. 167(10), 1232-1239.

Fucetola, R., Newcomer, J.W., Craft, S., Melson, A.K., 1999. Age- and dose-dependent glucose-induced increases in memory and attention in schizophrenia. Psychiat. Res. 88(1), 1-13.

Gatto, N.M., Henderson, V.W., St John, J.A., McCleary, C., Hodis, H.N., Mack, W.J., 2008. Metabolic syndrome and cognitive function in healthy middle-aged and older adults without diabetes. Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn. 15(5), 627-641.

Gluck, M.E., Ziker, C., Schwegler, M., Thearle, M., Votruba, S.B., Krakoff, J., 2013. Impaired glucose regulation is associated with poorer performance on the Stroop Task. Physiol. Behav. 122, 113-119.

Goldberg, T.E., Goldman, R.S., Burdick, K.E., Malhotra, A.K., Lencz, T., Patel, R.C., Woerner, M.G., Schooler, N.R., Kane, J.M., Robinson, D.G., 2007. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? Arch. Gen. Psychiat. 64(10), 1115-1122.

Gonzalez-Blanch, C., Crespo-Facorro, B., Alvarez-Jimenez, M., Rodriguez-Sanchez, J.M., Pelayo-Teran, J.M., Perez-Iglesias, R., Vazquez-Barquero, J.L., 2007. Cognitive dimensions in first-episode schizophrenia spectrum disorders. J. Psychiatr. Res. 41(11), 968-977.

Gonzalez-Blanch, C., Crespo-Facorro, B., Alvarez-Jimenez, M., Rodriguez-Sanchez, J.M., Perez-Iglesias, R., Pelayo-Teran, J.M., Martinez-Garcia, O., Vazquez-Barquero, J.L., 2008. Lack of association between clinical and cognitive change in first-episode psychosis: the first 6 weeks of treatment. Can. J.Psychiatry. 53(12), 839-847.

Green, M.F., Marder, S.R., Glynn, S.M., McGurk, S.R., Wirshing, W.C., Wirshing, D.A., Liberman, R.P., Mintz, J., 2002. The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. Biol. Psychiat. 51(12), 972-978.

Grundy, S.M., Cleeman, J.I., Daniels, S.R., Donato, K.A., Eckel, R.H., Franklin, B.A., Gordon, D.J., Krauss, R.M., Savage, P.J., Smith, S.C., Jr., Spertus, J.A., Costa, F., American Heart, A., National Heart, L., Blood, I., 2005. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 112(17), 2735-2752.

Gunstad, J., Paul, R.H., Cohen, R.A., Tate, D.F., Gordon, E., 2006. Obesity is associated with memory deficits in young and middle-aged adults. Eat Weight Disord. 11(1), e15-19.

Gunstad, J., Spitznagel, M.B., Paul, R.H., Cohen, R.A., Kohn, M., Luyster, F.S., Clark, R., Williams, L.M., Gordon, E., 2008. Body mass index and neuropsychological function in healthy children and adolescents. Appetite. 50(2-3), 246-251.

Gustafson, T.B., Sarwer, D.B., 2004. Childhood sexual abuse and obesity. Obes. Rev. 5(3), 129-135.

Hair, N.L., Hanson, J.L., Wolfe, B.L., Pollak, S.D., 2015. Association of Child Poverty, Brain Development, and Academic Achievement. JAMA Pediatr. 169(9), 822-829.

Harrison, S.L., Ding, J., Tang, E.Y., Siervo, M., Robinson, L., Jagger, C., Stephan, B.C., 2014. Cardiovascular disease risk models and longitudinal changes in cognition: a systematic review. PLOS ONE. 9(12), e114431.

Harvey, J., 2007. Leptin regulation of neuronal excitability and cognitive function. Curr. Opin. Pharmacol. 7(6), 643-647.

Harvey, P.D., Rabinowitz, J., Eerdekens, M., Davidson, M., 2005. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. Am. J. Psychiatry. 162(10), 1888-1895.

Hasnain, M., Fredrickson, S.K., Vieweg, W.V., Pandurangi, A.K., 2010. Metabolic syndrome associated with schizophrenia and atypical antipsychotics. Curr. Diab. Rep. 10(3), 209-216.

Hassenstab, J.J., Sweat, V., Bruehl, H., Convit, A., 2010. Metabolic syndrome is associated with learning and recall impairment in middle age. Dement. Geritr. Cogn. 29(4), 356-362.

Hepgul, N., Pariante, C.M., Dipasquale, S., DiForti, M., Taylor, H., Marques, T.R., Morgan, C., Dazzan, P., Murray, R.M., Mondelli, V., 2012. Childhood trauma is associated with increased Body Mass Index and increased C-reactive protein levels in first-episode psychosis patients. Psychol. Med. 42(9), 1893-1901.

Higgins, V., Adeli, K., 2017. Pediatric Metabolic Syndrome: Pathophysiology and Laboratory Assessment. EJIFCC. 28(1), 25-42.

Hill, S.K., Bishop, J.R., Palumbo, D., Sweeney, J.A., 2010. Effect of second-generation antipsychotics on cognition: current issues and future challenges. Expert Rev. Neurother. 10(1), 43-57.

Hill, S.K., Keshavan, M.S., Thase, M.E., Sweeney, J.A., 2004. Neuropsychological dysfunction in antipsychotic-naive first-episode unipolar psychotic depression. Am. J. Psychiatry. 161(6), 996-1003.

Johnsen, E., Fathian, F., Kroken, R.A., Steen, V.M., Jørgensen, H.A., Gjestad, R., Løberg, E.-M., 2016. The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis. BMC Psychiatry. 16(1), 60.

Kaplan, G.A., Turrell, G., Lynch, J.W., Everson, S.A., Helkala, E.L., Salonen, J.T., 2001. Childhood socioeconomic position and cognitive function in adulthood. Int. J. Epidemiol. 30(2), 256-263.

Kasai, K., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Lee, C.U., Ciszewski, A.A., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003. Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. Am. J. Psychiatry. 160(1), 156-164.

Keefe, R.S., 1995. The contribution of neuropsychology to psychiatry. Am. J. Psychiatry. 152(1), 6-15.

Keefe, R.S., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., Coughenour, L., 2004. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr. Res. 68(2-3), 283-297.

Keefe, R.S., Harvey, P.D., 2012. Cognitive impairment in schizophrenia. Handb. Exp. Pharmacol. (213), 11-37.

Kuroki, N., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Onitsuka, T., Ersner-Hershfield, H., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2006. Middle and inferior temporal gyrus gray matter volume abnormalities in first-episode schizophrenia: an MRI study. Am. J. Psychiatry. 163(12), 2103-2110.

Lamport, D.J., Lawton, C.L., Mansfield, M.W., Dye, L., 2009. Impairments in glucose tolerance can have a negative impact on cognitive function: a systematic research review. Neurosci. Biobehav. R. 33(3), 394-413.

Lande, M.B., Kupferman, J.C., 2015. Cognitive function in hypertensive children. Curr. Hypertens. Rep. 17(1), 508.

Lavie, C.J., Milani, R.V., Ventura, H.O., 2009. Obesity and Cardiovascular Disease. J. Am. Coll. Cardiol. 53(21), 1925-1932.

Leeson, V.C., Harrison, I., Ron, M.A., Barnes, T.R., Joyce, E.M., 2012. The effect of cannabis use and cognitive reserve on age at onset and psychosis outcomes in first-episode schizophrenia. Schizophr. Bull. 38(4), 873-880.

Li, C., Zhan, G., Rao, S., Zhang, H., 2014. Metabolic syndrome and its factors affect cognitive function in chronic schizophrenia complicated by metabolic syndrome. J. Nerv. Ment. Dis. 202(4), 313-318.

Liang, J., Matheson, B.E., Kaye, W.H., Boutelle, K.N., 2014. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int. J. Obes. (Lond). 38(4), 494-506.

Lindenmayer, J.P., Khan, A., Kaushik, S., Thanju, A., Praveen, R., Hoffman, L., Cherath, L., Valdez, G., Wance, D., 2012. Relationship between metabolic syndrome and cognition in patients with schizophrenia. Schizophr. Res. 142(1-3), 171-176.

Lorenz, W.F., 1922. Sugar Tolerance in Dementia Praecox and Other Mental Disorders. Arch. NeurPsych. 8(2), 184.

Lutgens, D., Lepage, M., Iyer, S., Malla, A., 2014. Predictors of cognition in first episode psychosis. Schizophr. Res. 152(1), 164-169.

Malik, A.B., Shuaib, A., Turner, M.E., 2017. Neuropsychological Evaluation. http://emedicine.medscape.com/article/317596-overview.

Martinez-Cengotitabengoa, M., Mac-Dowell, K.S., Leza, J.C., Mico, J.A., Fernandez, M., Echevarria, E., Sanjuan, J., Elorza, J., Gonzalez-Pinto, A., 2012. Cognitive impairment is related to oxidative stress and chemokine levels in first psychotic episodes. Schizophr. Res. 137(1-3), 66-72.

McCleery, A., Addington, J., Addington, D., 2006. Substance misuse and cognitive functioning in early psychosis: a 2 year follow-up. Schizophr. Res. 88(1-3), 187-191.

McElroy, S.L., 2009. Obesity in patients with severe mental illness: overview and management. J. Clin. Psychiatry. 70 Suppl 3, 12-21.

McEvoy, J.P., Meyer, J.M., Goff, D.C., Nasrallah, H.A., Davis, S.M., Sullivan, L., Meltzer, H.Y., Hsiao, J., Scott Stroup, T., Lieberman, J.A., 2005. Prevalence of the metabolic syndrome in patients with

schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr. Res. 80(1), 19-32.

McGurk, S.R., Mueser, K.T., 2004. Cognitive functioning, symptoms, and work in supported employment: a review and heuristic model. Schizophr. Res. 70(2-3), 147-173.

Meikle, A., Riby, L.M., Stollery, B., 2004. The impact of glucose ingestion and gluco-regulatory control on cognitive performance: a comparison of younger and middle aged adults. Hum. Psychopharmacol. 19(8), 523-535.

Messier, C., Awad-Shimoon, N., Gagnon, M., Desrochers, A., Tsiakas, M., 2011. Glucose regulation is associated with cognitive performance in young nondiabetic adults. Behav. Brain Res. 222(1), 81-88.

Minzenberg, M.J., Laird, A.R., Thelen, S., Carter, C.S., Glahn, D.C., 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch. Gen. Psychiat. 66(8), 811-822.

Mitchell, A.J., Vancampfort, D., De Herdt, A., Yu, W., De Hert, M., 2013. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. Schizophr. Bull. 39(2), 295-305.

Moore, J.X., Chaudhary, N., Akinyemiju, T., 2017. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. Prev. Chronic Dis. 14, E24.

Morgan, V.A., Badcock, J., Waterreus, A., Galletly, C., Shah, S., Mackinnon, A., 2014. The role of cognition in metabolic disturbance in people with psychotic illness: Novel data from a large population prevalence survey. Schizophr. Res. 153, S223-S224.

Mortby, M.E., Janke, A.L., Anstey, K.J., Sachdev, P.S., Cherbuin, N., 2013. High "normal" blood glucose is associated with decreased brain volume and cognitive performance in the 60s: the PATH through life study. PLOS ONE. 8(9), e73697.

Nagel, B.J., Herting, M.M., Maxwell, E.C., Bruno, R., Fair, D., 2013. Hemispheric lateralization of verbal and spatial working memory during adolescence. Brain Cogn. 82(1), 58-68.

Naguib, J.M., Kulinskaya, E., Lomax, C.L., Garralda, M.E., 2009. Neuro-cognitive performance in children with type 1 diabetes--a meta-analysis. J. Pediatr Psychol. 34(3), 271-282.

Nasrallah, H.A., 2010. Linkage of cognitive impairments with metabolic disorders in schizophrenia. Am. J. Psychiatry. 167(10), 1155-1157.

Nelson, R.A., Bremer, A.A., 2010. Insulin resistance and metabolic syndrome in the pediatric population. Metab. Syndr. Relat. D. 8(1), 1-14.

Newcomer, J.W., Craft, S., Fucetola, R., Moldin, S.O., Selke, G., Paras, L., Miller, R., 1999. Glucose-induced increase in memory performance in patients with schizophrenia. Schizophr. Bull. 25(2), 321-335.

Newcomer, J.W., Haupt, D.W., Fucetola, R., Melson, A.K., Schweiger, J.A., Cooper, B.P., Selke, G., 2002. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. Arch. Gen. Psychiat. 59(4), 337-345.

Noble, K.G., Norman, M.F., Farah, M.J., 2005. Neurocognitive correlates of socioeconomic status in kindergarten children. Developmental Sci. 8(1), 74-87.

Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., Heaton, R.K., 2004. Identification of separable cognitive factors in schizophrenia. Schizophr. Res. 72(1), 29-39.

Nuechterlein, K.H., Dawson, M.E., 1984. Information processing and attentional functioning in the developmental course of schizophrenic disorders. Schizophr. Bull. 10(2), 160-203.

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese, F.J., 3rd, Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry. 165(2), 203-213.

Ohmann, S., Popow, C., Rami, B., Konig, M., Blaas, S., Fliri, C., Schober, E., 2010. Cognitive functions and glycemic control in children and adolescents with type 1 diabetes. Psychol. Med. 40(1), 95-103.

Owen, L., Scholey, A., Finnegan, Y., Sunram-Lea, S.I., 2013. Response variability to glucose facilitation of cognitive enhancement. Brit. J. Nutr. 110(10), 1873-1884.

Owen, L., Scholey, A.B., Finnegan, Y., Hu, H., Sunram-Lea, S.I., 2012. The effect of glucose dose and fasting interval on cognitive function: a double-blind, placebo-controlled, six-way crossover study. Psychopharmacology (Berl). 220(3), 577-589.

Palmisano, G.L., Innamorati, M., Vanderlinden, J., 2016. Life adverse experiences in relation with obesity and binge eating disorder: A systematic review. J. Behav. Addict. 5(1), 11-31.

Panza, F., Frisardi, V., Capurso, C., Imbimbo, B.P., Vendemiale, G., Santamato, A., D'Onofrio, G., Seripa, D., Sancarlo, D., Pilotto, A., Solfrizzi, V., 2010. Metabolic syndrome and cognitive impairment: current epidemiology and possible underlying mechanisms. J. Alzheimers Dis. 21(3), 691-724.

Papanastasiou, E., 2013. The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. Ther. Adv. Psychopharmacol. 3(1), 33-51.

Pavlik, V.N., Hyman, D.J., Doody, R., 2005. Cardiovascular risk factors and cognitive function in adults 30-59 years of age (NHANES III). Neuroepidemiology. 24(1-2), 42-50.

Pencer, A., Addington, J., 2003. Substance use and cognition in early psychosis. J. Psychiatr. Neurosci. 28(1), 48-54.

Pettersson-Yeo, W., Benetti, S., Marquand, A.F., Dell'acqua, F., Williams, S.C., Allen, P., Prata, D., McGuire, P., Mechelli, A., 2013. Using genetic, cognitive and multi-modal neuroimaging data to identify ultra-high-risk and first-episode psychosis at the individual level. Psychol. Med. 43(12), 2547-2562.

Pettersson-Yeo, W., Benetti, S., Marquand, A.F., Joules, R., Catani, M., Williams, S.C., Allen, P., McGuire, P., Mechelli, A., 2014. An empirical comparison of different approaches for combining multimodal neuroimaging data with support vector machine. Front. Neurosci-Switz. 8, 189.

Popkin, M.K., Colon, E.A., 2001. The interface of psychiatric disorders and diabetes mellitus. Curr. Psychiat. Rep. 3(3), 243-250.

Potvin, S., Joyal, C.C., Pelletier, J., Stip, E., 2008. Contradictory cognitive capacities among substance-abusing patients with schizophrenia: a meta-analysis. Schizophr. Res. 100(1-3), 242-251.

Purdon, S.E., Jones, B.D., Stip, E., Labelle, A., Addington, D., David, S.R., Breier, A., Tollefson, G.D., 2000. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. Arch. Gen. Psychiat. 57(3), 249-258.

Rabin, R.A., Zakzanis, K.K., George, T.P., 2011. The effects of cannabis use on neurocognition in schizophrenia: a meta-analysis. Schizophr. Res. 128(1-3), 111-116.

Rao, D.P., Dai, S., Lagace, C., Krewski, D., 2014. Metabolic syndrome and chronic disease. Chronic Dis. Inj. Can. 34(1), 36-45.

Raphael, T., Parsons, J., 1921. Blood Sugar Studies in Dementia Praecox and Manic-Depressive Insanity. Arch. NeurPsych. 5(6), 687-709.

Rapp, C., Studerus, E., Bugra, H., Aston, J., Tamagni, C., Walter, A., Pflueger, M., Borgwardt, S., Riecher-Rossler, A., 2013. Duration of untreated psychosis and cognitive functioning. Schizophr. Res. 145(1-3), 43-49.

Riediger, N.D., Clara, I., 2011. Prevalence of metabolic syndrome in the Canadian adult population. Can. Med. Assoc. J. 183(15), E1127-1134.

Robinson, H., Calamia, M., Glascher, J., Bruss, J., Tranel, D., 2014. Neuroanatomical correlates of executive functions: a neuropsychological approach using the EXAMINER battery. J. Int. Neuropsych. Soc. 20(1), 52-63.

Roper, L.J., Purdon, S.E., Aitchison, K.J., 2015. Childhood and later life stressors and psychosis. Clin. Neuropsychiatry J. Treat. Eval. 12(6), 148.

Rund, B.R., Melle, I., Friis, S., Larsen, T.K., Midboe, L.J., Opjordsmoen, S., Simonsen, E., Vaglum, P., McGlashan, T., 2004. Neurocognitive dysfunction in first-episode psychosis: correlates with symptoms, premorbid adjustment, and duration of untreated psychosis. Am. J. Psychiatry. 161(3), 466-472.

Scholes, K.E., Martin-Iverson, M.T., 2010. Cannabis use and neuropsychological performance in healthy individuals and patients with schizophrenia. Psychol. Med. 40(10), 1635-1646.

Segura, B., Jurado, M.A., Freixenet, N., Albuin, C., Muniesa, J., Junque, C., 2009. Mental slowness and executive dysfunctions in patients with metabolic syndrome. Neurosci. Lett. 462(1), 49-53.

Setayeshgar, S., Whiting, S.J., Vatanparast, H., 2012. Metabolic syndrome in canadian adults and adolescents: prevalence and associated dietary intake. ISRN Obes. 2012, 816846.

Shams, T.A., Muller, D.J., 2014. Antipsychotic induced weight gain: genetics, epigenetics, and biomarkers reviewed. Curr. Psychiat. Rep. 16(10), 473.

Smith, M.A., Riby, L.M., Eekelen, J.A., Foster, J.K., 2011. Glucose enhancement of human memory: a comprehensive research review of the glucose memory facilitation effect. Neurosci. Biobehav. R. 35(3), 770-783.

Sponheim, S.R., Jung, R.E., Seidman, L.J., Mesholam-Gately, R.I., Manoach, D.S., O'Leary, D.S., Ho, B.C., Andreasen, N.C., Lauriello, J., Schulz, S.C., 2010. Cognitive deficits in recent-onset and chronic schizophrenia. J. Psychiatr. Res. 44(7), 421-428.

Sumiyoshi, T., 2008. Possible dose-side effect relationship of antipsychotic drugs: relevance to cognitive function in schizophrenia. Expert Rev. Clin. Phar. 1(6), 791-802.

Taylor, V.H., MacQueen, G.M., 2007. Cognitive dysfunction associated with metabolic syndrome. Obes. Rev. 8(5), 409-418.

Taylor, V.H., McIntyre, R.S., Remington, G., Levitan, R.D., Stonehocker, B., Sharma, A.M., 2012. Beyond pharmacotherapy: understanding the links between obesity and chronic mental illness. Can. J. Psychiatry. 57(1), 5-12.

Thiebaut de Schotten, M., Dell'Acqua, F., Forkel, S.J., Simmons, A., Vergani, F., Murphy, D.G., Catani, M., 2011. A lateralized brain network for visuospatial attention. Nat. Neurosci. 14(10), 1245-1246.

Thiebaut de Schotten, M., Dell'Acqua, F., Ratiu, P., Leslie, A., Howells, H., Cabanis, E., Iba-Zizen, M.T., Plaisant, O., Simmons, A., Dronkers, N.F., Corkin, S., Catani, M., 2015. From Phineas Gage and Monsieur Leborgne to H.M.: Revisiting Disconnection Syndromes. Cereb Cortex. 25(12), 4812-4827.

Toalson, P., Ahmed, S., Hardy, T., Kabinoff, G., 2004. The Metabolic Syndrome in Patients With Severe Mental Illnesses. Prim. Care. Companion J. Clin. Psychiatry. 6(4), 152-158.

Tournoy, J., Lee, D.M., Pendleton, N., O'Neill, T.W., O'Connor, D.B., Bartfai, G., Casanueva, F.F., Finn, J.D., Forti, G., Giwercman, A., Han, T.S., Huhtaniemi, I.T., Kula, K., Lean, M.E., Moseley, C.M., Punab, M., Silman, A.J., Vanderschueren, D., Wu, F.C., Boonen, S., group, E.s., 2010. Association of cognitive performance with the metabolic syndrome and with glycaemia in middle-aged and older European men: the European Male Ageing Study. Diabetes Metab. Res. Rev. 26(8), 668-676.

Troisi, A., 2009. Cholesterol in coronary heart disease and psychiatric disorders: same or opposite effects on morbidity risk? Neurosci. Biobehav. R. 33(2), 125-132.

van den Berg, E., Kloppenborg, R.P., Kessels, R.P., Kappelle, L.J., Biessels, G.J., 2009. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. Biochim. Biophys. Acta. 1792(5), 470-481.

Vancampfort, D., Correll, C.U., Galling, B., Probst, M., De Hert, M., Ward, P.B., Rosenbaum, S., Gaughran, F., Lally, J., Stubbs, B., 2016. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry. 15(2), 166-174.

Vancampfort, D., Wampers, M., Mitchell, A.J., Correll, C.U., De Herdt, A., Probst, M., De Hert, M., 2013. A meta-analysis of cardio-metabolic abnormalities in drug naive, first-episode and multi-episode patients with schizophrenia versus general population controls. World Psychiatry. 12(3), 240-250.

Vieira, J.R., Elkind, M.S., Moon, Y.P., Rundek, T., Boden-Albala, B., Paik, M.C., Sacco, R.L., Wright, C.B., 2011. The metabolic syndrome and cognitive performance: the Northern Manhattan Study. Neuroepidemiology. 37(3-4), 153-159.

Weickert, T.W., Goldberg, T.E., Marenco, S., Bigelow, L.B., Egan, M.F., Weinberger, D.R., 2003. Comparison of cognitive performances during a placebo period and an atypical antipsychotic treatment period in schizophrenia: critical examination of confounds. Neuropsychopharmacol. 28(8), 1491-1500.

Wolf, P.A., Beiser, A., Elias, M.F., Au, R., Vasan, R.S., Seshadri, S., 2007. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. Curr. Alzheimer Res. 4(2), 111-116.

Yates, K.F., Sweat, V., Yau, P.L., Turchiano, M.M., Convit, A., 2012. Impact of metabolic syndrome on cognition and brain: a selected review of the literature. Arterioscl. Throm. Vas. 32(9), 2060-2067.

Yau, P.L., Castro, M.G., Tagani, A., Tsui, W.H., Convit, A., 2012. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics. 130(4), e856-864.

Yucel, M., Bora, E., Lubman, D.I., Solowij, N., Brewer, W.J., Cotton, S.M., Conus, P., Takagi, M.J., Fornito, A., Wood, S.J., McGorry, P.D., Pantelis, C., 2012. The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. Schizophr. Bull. 38(2), 316-330.

Yuste, R., 2015. From the neuron doctrine to neural networks. Nat. Rev. Neurosci. 16(8), 487-497.

Zimmet, P., Alberti, K.G., Kaufman, F., Tajima, N., Silink, M., Arslanian, S., Wong, G., Bennett, P., Shaw, J., Caprio, S., Group, I.D.F.C., 2007. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr. Diabetes. 8(5), 299-306.

4. "Non-verbal cognitive domain functions positively associate with mildly elevated fasting blood glucose in individuals presenting with a psychotic illness."

Manuscript Title

Domain Specific MCCB-assessed cognitive associations to symptoms of metabolic syndrome in patient referred to an early psychosis intervention clinic.

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Abstract

Objectives: Metabolic syndrome (MetS) is a cluster of clinical markers identified as significant risk factors in the development of cardiovascular disease, which is associated with psychiatric populations by independent connections via the taking of medications and having a severe mental illness (SMI). This study is an exploration of the relationships between MetS (and its markers) and cognitive functioning in a relatively young population with a psychotic illness.

Methods: Forty-seven individuals presenting in the early phase of psychosis to the Edmonton Early Psychosis Intervention Clinic, in Alberta, Canada, were assessed with the MATRICS Consensus Cognitive Battery. Clinical assessment also included an evaluation of the markers of MetS. Following an exploratory analysis, linear regression analysis was used to examine possible significant relationships between discrete markers of MetS and specific cognitive domains.

Results: Fasting blood glucose levels within the normal range were positively associated with spatial working memory (p = 0.02), learning and memory of designs (p = 0.04), and spatial reasoning and problem solving (p = 0.02). Medication effects were also noted. Other covariates did not exert any significant effect on these relationships.

Conclusions: The consistency of the relationships across non-verbal instruments suggests a potentially reliable effect that may implicate relatively circumscribed cerebral effects of glucose in relation to relevant neurobiology. Although provocative, replication will be necessary to gain confidence in the stability of this result and the validity of inferences regarding potential mechanisms that might underlie this association.

Keywords: Cognition, spatial working memory, non-verbal memory, reasoning and problem solving, MATRICS, MCCB, metabolic syndrome, glucose, psychosis.

Background

There is limited information available that looks at early cognitive changes in young individuals with severe mental illness (SMI) in the context of metabolic syndrome (MetS). Since these individuals already suffer cognitive impairment as a result of having SMI, they may be at increased vulnerability of further impairment as a result of developing MetS or a dysfunction in one of its markers. Poor cognitive functioning, along with the increased cardiometabolic risk can result in decreased quality of life and increased mortality.

MetS is a constellation of cardiovascular risk factors that includes obesity, dysglycemia, dylipidemia (i.e., decreased serum high density lipoprotein (HDL) cholesterol, elevated serum triglycerides), and hypertension (HTN). Criteria have been proposed by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) (2002), and by the International Diabetes Foundation (IDF), with harmonised criteria being proposed in a joint statement (Table 1).[1-3]

In young adult populations, the prevalence of MetS in the general population (4.2% - 18.6% depending on criteria used) appears to approximate the prevalence found amongst similarly aged individuals with SMI (3.9% - 15.9% depending on criteria used). The prevalence rate of MetS in older adults with SMI rises to 36.7% *vs.* 23.7% in the general U.S. adult population which suggests that both developing SMI and the treatment of the same with antipsychotic medications are risk factors for MetS.[4-8]

MetS has also been associated with the development of dementia in older populations, suggesting a link between MetS and cognitive impairment.[9] More recent research involving

non-geriatric populations has suggested an association between MetS and deficits in memory, executive functioning, processing speed and general intellect.[10-19] In a young population, Yau et al. (2012) showed that individuals (age 14 – 20 years) with MetS appear to have impairments in attention, mental flexibility (an executive function), and general intellect.[20]

Many studies have focused on the roles of obesity and glucose dysregulation since both of these factors have been proposed as being responsible for the perturbations observed in MetS. More specifically, in the general population, obesity appeared to be negatively associated with executive functioning and attention, with some studies also suggesting an impact on visuospatial skills.[15, 21, 22] Diabetes appears to be associated with impairments in executive functioning, processing speed, and attention.[15, 23] Non-diabetic individuals with slightly impaired glucose regulation (blood glucose > 5.6 mmol/l and <7.01 mmol/l), however, appeared to show some cognitive benefits with glucose supplementation, suggesting a possible inverted U-shaped relationship between cognitive functioning and glucose regulation.[24-26]

The research looking at how MetS may contribute to the development of dementia has raised similar questions with respect to the cognitive functioning of individuals with SMI. Individuals with SMI already appear to have cognitive impairments that are present in both active and stable phases of illness, with the severity of the deficits ranging between ~0.5 and ~3 standard deviations below the norm.[27-29] Individuals with schizophrenia appear to have greater deficits than those with other forms of SMI and other diagnoses such as mood disorders.[30, 31]

Individuals having both psychosis and MetS appear to demonstrate greater cognitive deficits when compared to those with psychosis but without MetS.[32-34] A recent study suggested that

even in a relatively young group (mean age 30 years), a similar direct association between cognitive deficits and cardiovascular risk may be present; however, there was no discussion regarding the relationship between the particular factors of MetS and dysfunction in specific cognitive domains.[35]

There has been very little discussion about how these factors may play a role early in the course of SMI. Characterising the relationships between MetS and cognitive functioning in the early stages of SMI may suggest interventions to protect cognitive functioning, and in turn, may lead to improved long term outcomes in mortality and morbidity. This study aims to examine the relationship between MetS and cognitive functioning in a younger, Canadian population presenting with First Episode Psychosis (FEP).

Methods

Human Research Ethics Board Statement

This study was reviewed and approved by the University of Alberta Human Research Ethics Board. The requirement to obtain patient consent was waived because much of the sample under investigation was no longer available to provide consent.

Population

The sample consisted of anonymised archival data from individuals presenting to the Edmonton Early Psychosis Intervention Clinic (EEPIC) in Edmonton, Alberta, Canada. Referral criteria for this service are that the individual be between ages 16 years and 35 years, experiencing

symptoms of a psychotic illness, and having less than a year of exposure to antipsychotic treatment prior to entry into the service.

Assessment

The data were extracted from a broader archival review of Alberta Hospital Edmonton (AHE) Neuropsychology Department records from patients presenting for routine clinical evaluations between December of 2001 and March of 2015. The initial evaluation was undertaken within the AHE Neuropsychology Department either by or under the direction of a registered clinical neuropsychologist. The assessment consisted of a clinical interview that included a Structured Clinical Interview for DSM IV-TR diagnosis (SCID-I) (Biometrics Research, 2002), clinician- and patient-rated symptoms of psychosis, mood, anxiety, motor signs, and adverse effects of medication, as well as a series of performance-based tests of cognitive function.

Other data such as demographic variables, blood pressure, weight, height, and waist circumference were also collected at this visit along with fasting blood work (fasting blood glucose, fasting serum triglycerides, and fasting serum HDL cholesterol) and urine samples. The primary medication being used for treatment was recorded and consideration was given for the role that medication might play in the subject's metabolic and cognitive profile.

Cognitive function was assessed using the MATRICS Consensus Cognitive Battery (MCCB) which assesses the following domains: speed of processing (BACS: Symbol Coding, Category Fluency: Animal Naming, Trail Making Test: Part A); attention/vigilance (CPT-IP); working memory (WMS®-III: Spatial Span; Letter-Number Span); verbal learning (HVLT-R™); visual learning (BVMT-R™); reasoning and problem solving (NAB®: Mazes).[36-38] The MCCB assessment for

measuring social cognition was not included in this neuropsychological evaluation. T-scores were computed for each scale, and were age and gender adjusted against established normative data using the software provided with the MCCB. An average of the T-scores across the subscales provided a global score for analysis (MCCB-Total).

Statistical Analysis

Statistical analysis was completed using IBM SPSS Statistics 24 (IBM, 2016). Normality of the data was inspected. Analysis was initially completed using MCCB-Total scores and identifying correlations (Pearson's *r*) with components of MetS. Further sub-analysis investigated the relationships (Pearson's *r*) between the specific MCCB subscales scores and the components of MetS. One-way ANOVAs were used to explore the role of possible confounders (medication, cannabis use in the last 30, occupational status, years of education, socio-economic status (SES), and duration of antipsychotic treatment prior to assessment) given the possible impact that these parameters may have on performance in cognitive assessments.[38-41] Medications were grouped into a categorical variable of low, medium and high metabolic impact based on prior data.[42, 43] Where confounders were found to have a significant or a trend level effect in the ANOVAs, they were taken forward into linear regression models, each with a cognitive assessment T-score as the dependent variable and predictors including fasting glucose, and any confounders as above.

Corrections for multiple testing were done through the Benjamini-Hochberg method with the false discovery rate set at 0.10.[44]

Results

Study Population

Forty-seven subjects were included in the final analysis (Table 2). The mean age of the group was 22.6 years (*sd* 4.6 years), with 72% being male. One individual was 36 years old, but included on an exception basis as they were also offered clinical follow-up. The mean length of continuous pharmacological treatment with any antipsychotic just prior to the initial assessment was 69.4 days (*median* 31.0 days; *sd* 95.1 days). Diagnoses included schizophrenia spectrum disorders, substance induced psychosis, mood disorders with psychotic features, and anxiety disorders.

Metabolic Profile of Study Population

As only two individuals (4.3%) met criteria for MetS as defined by NCEP-ATP III criteria (Table 3), the analysis examined relationships between the discrete markers of MetS and specific cognitive domains. Twelve subjects had decreased HDL cholesterol levels, 13 subjects had elevated serum triglyceride levels, 11 subjects had hypertension, and 6 subjects had an increased waist circumference. There was no incidence of elevated fasting blood glucose, as defined by the NCEP-ATP III criteria (when using IDF criteria, 8% met criteria for impaired glucose tolerance).

Cognitive – Metabolic Relationships

An initial correlation analysis was completed using MCCB-Total and the factors of MetS. A significant positive relationship was noted between fasting blood glucose values and MCCB-

Total (r = 0.29; p = 0.05). Further analysis inspected the relationship between MCCB subscales and fasting blood glucose and revealed significant positive associations with a spatial working memory task (r = 0.34; p = 0.02), a spatial reasoning and problem solving task (r = 0.34; p = 0.02), and a visual learning task (r = 0.32; p = 0.03). No significant relationships were noted between MCCB-Total and the MCCB subscales with measures of obesity.

From the ANOVA analysis, medication was found to affect the relationship between MCCB-Total and fasting blood glucose ($p < 0.01$), and a trend was noted the role that medication played in the relationships involving the task of spatial working memory (p = 0.11) and the task of visual learning (p = 0.10). Occupational status, years of education, and duration of medication exposure appeared to have at least a trend level effect on MCCB-Total, but this did not persist into the relationships involving fasting blood glucose and was not significant in the final linear regression model involving MCCB-Total. SES and cannabis use were not significantly associated with any of the cognitive measures. The results of the linear regression analyses are shown in Table 4.

Discussion

Few studies have investigated the relationship between the factors of MetS and the domains of cognitive functioning in a population of individuals presenting with first episode psychosis. The rates of MetS and abnormal markers of MetS were similar to those described in the general population for a similar age group;[45-48] this was in keeping with a previous study involving subjects with FEP.[49] It was also noted that the rates of abnormal findings increased noticeably

in the first 6 to 12 months of treatment.[45, 49] At EEPIC, we have a relatively young population, and typically, one expects the rates of MetS to increase with age and duration of treatment.

General Cognition

The overall cognitive performance of our population revealed scores up to 1.5 standard deviations below the norms of the general population. There was some variation noted in the different domains as measured by the MCCB, with the greatest deficits present in areas of processing speed (BACS Symbol Coding), verbal learning (HVLT-R), and working memory (CPT-IP) (Figure 1). This is consistent with previous findings where deficits have been noted in areas of working memory, verbal learning, processing speed, and executive functioning,[27, 29, 50] and is also similar to findings in populations of individuals with chronic psychotic illnesses.[51-53] This suggests that much of the cognitive dysfunction is present at the onset or possibly even before the first episode of psychosis. Other factors include the age of illness onset and severity of negative symptoms given the postulated interference with cognitive development in early to mid adolescence.[54, 55] One could consider that the developmental changes (due to various possible aetiologies) over the course of adolescence that lead to FEP also alter cognitive functioning, and represent a relative deficit when compared to what might have occurred if one's brain had developed along a "normal" trajectory.

Cognitive performance relating to fasting glucose

Previous studies have suggested that impaired fasting glucose negatively affected processing speed and attention.[15, 23] We did not find such associations in our sample. One possible reason for this may have been that the low prevalence of impaired glucose regulation in our sample

(0% using NCEP-ATP III criteria; 8% using IDF criteria) did not generate a sufficient range of scores; the severity of the cognitive dysfunction in previous studies was assessed by comparing individuals with abnormal fasting blood glucose against individuals without. The differences in our sample (e.g. age range, comorbidities) and methodology may explain the absence of these previous findings.

Interestingly, we observed that higher fasting blood glucose levels within the usually normal range (3.3 mmol/l - 6.0 mmol/l) appeared to demonstrate significant positive associations with the non-verbal cognitive domains of spatial problem solving and reasoning (NAB®: Mazes), non-verbal working memory (WMS®-III: Spatial Span), and visual learning (BVMT-R™). This appears to be a unique finding not previously reported. Improved performance in working memory and problem solving has been correlated with processing speed, and working memory with attention within the MCCB;[38] however, our sample did not show these same associations, possibly indicating that there may be an independent mechanism for our result. It is unclear if the results from the studies involving random blood glucose can be extended to fully explain our finding, but there is a suggestion that glucose activity in the hippocampus should be considered, perhaps in conjunction with other cellular mechanisms involving insulin and insulin receptor (IR) activity. Also, given the domains associated with fasting blood glucose in our study, one might postulate that there may be a regional or hemispheric mechanism.

Caravaggia et al. (2015) has suggested that elevated peripheral insulin levels (as a result of increased peripheral glucose) may result in increased insulin concentration in the brain which would result in the activation of more IRs. In individuals with schizophrenia, there appears to

be a general reduction of insulin receptor concentration, not entirely attributable to antipsychotic use.[56] If individuals with schizophrenia have reduced insulin receptor concentrations, then to activate the hippocampal neurons to support learning functions, there would need to be increased glucose requirements, and this may partially explain the results noted in our sample. The increased glucose needs may be met by dietary intake. Greenwood and Winocur (2005) suggest that improved cognitive performance due to glucose intake is more noticeable in individuals that already have a lower baseline level of cognitive functioning, with a more robust response noted in individuals with mild insulin resistance (versus in those with normal insulin activity), and that this effect was no longer evident in individuals meeting criteria for diabetes.[57]

The non-verbal cognitive domains of problem solving and reasoning, non-verbal working memory, and visual learning are generally associated with right hemispheric processes. Variations in blood flow have often been used as an indirect marker of brain activity, which is also associated with the neuronal uptake of glucose. Wendt and Risberg (1994) noted that individuals utilizing a "right hemispheric approach" to spatial problem solving performed better on these tasks, and noted an associated increase in right hemispheric blood flow.[58] A 2002 study demonstrated increased right sided cerebral blood flows in patient with schizophrenia during passive visual tasks.[59] In addition, right-hemispheric processing benefits have been noted when on antipsychotic medication.[60, 61] These studies should be interpreted in the context of the finding of left hemisphere "overactivation", perhaps as compensation to impaired function, which appears to be the baseline of individuals with schizophrenia.[61, 62] In our population, where most subjects were medicated at the time of assessment, we may be

able to interpret our findings as a "restoration" of right sided processes that are then further enhanced by increased glucose availability.

Considering the above, it is possible to postulate that the relationship observed in this sample may be due to a mechanism where individuals with impaired cognitive functioning owing to having an SMI, and also having a slight degree of insulin resistance, are having a greater response to glucose ingestion (either through glucose directly or an appropriate meal near the time of assessment), resulting in a relatively mild enhancement in cognitive performance. The rate of cerebral blood flow through the right hemisphere increases to a greater degree compared to the left hemisphere during tasks of spatial problem solving. This would allow for increased glucose delivery to glucose and insulin sensitive structures in the right hemisphere (such as the medial temporal lobe),[63] and provide a mechanism for the observed greater performance in the non-verbal cognitive domains associated with the right hemisphere. A similar performance improvement in tasks related to the cognitive domains associated with the left hemisphere may not be noted owing to the already "overactive" left hemispheric cerebral blood flow in individuals with psychosis, which does not alter significantly during cognitive tasks.

Cognitive performance associated with obesity

We did not find any correlation between obesity and performance on the MCCB. While previous studies have demonstrated significant cognitive deficits in obese individuals, it should be noted that there are inconsistencies in the affected domains. A previous review by Liang et al. (2014) examined the literature regarding the cognitive deficits in obese children and

adolescents found that the evidence appeared mixed with respect to general cognitive functioning, language, learning, memory, and academic achievement.[22]

Role of other possible contributing factors

Medication use has been associated with metabolic changes in as little as six weeks of treatment and so it was somewhat unexpected that this was not significantly associated in our data.[45, 64, 65] Duration of pharmacotherapy has also been associated with improvements in cognitive performance, with Snyder et al. (2008) suggesting that as little as one month of treatment with an atypical antipsychotic can help resolve previously noted deficiencies in spatial working memory and problem solving.[40] In contrast, another study using a population of matched controls noted no significant improvement over a 6 week period of treatment.[66] Given the mixed results of these previous studies, our finding of there being no significant impact could have been due to the relatively short period of treatment noted above, and therefore, medication effects, either positive or negative may not show up by the time of assessment. In our study, this limitation may be in part due to the relatively large range in the duration of medication exposure (0 – 350 days). Unfortunately, for individuals already on medication, non-medicated baseline data for metabolic parameters was unavailable, and so initial changes may not have been detected.

Strengths and Limitations

Sample size is an obvious limitation; however, we took steps to address this by using the Benjamini-Hochberg method which can help increase a study's power compared to other methods of correcting for multiple analyses, by allowing for a greater false discovery rate.

Other limitations include potentially difficult to measure confounders such as the quality and quantity of sleep the night before, and environmental factors related to the location of the assessment.

One of the strengths of this study was the use of the MCCB. The MCCB is a robust cognitive battery that has been gaining wide acceptance. There are certain assumptions made in the interpretation of these results. Keefe (1995) described several such assumptions: neuropsychological tests measure specific functions, and poor performance on a single test indicates a specific neuropsychological deficit; abnormal neuropsychological test performance indicates specific regional brain dysfunction; "hypoactivity" during functional imaging procedures with cognitive activation tasks suggests regional brain dysfunction.[67]

The MCCB attempts to address these assumptions by using a battery of assessments. The selected assessments have some overlap (as evidenced by the partial correlation of performance) and so similar performance across several tests can allow one to draw better conclusions about neurological functioning. This appears to support our finding of the consistency in the associations identified between cognitive measures of a visuospatial nature.

Another strength was that the effort on the part of the participant was assessed; the majority of subjects were felt to have good effort. As part of the overall initial assessment, the subject is invited to participate in the neuropsychological assessment on a voluntary basis, and so it can be presumed that those subjects who took part were also reasonably motivated. Nonetheless, it will be important to replicate these findings in larger early psychosis samples.

Conclusions and Future Directions

In this sample of patients with early psychosis, high normal levels of fasting glucose were associated with improved cognitive performance on the MCCB, and more specifically, were positively related to non-verbal tasks including spatial working memory, recall of figures, and problem solving with mazes. There was no similar relationship to tasks of attention and processing speed.

These findings can serve as part of a baseline profile against which symptom progression can be measured and interventions can be evaluated. Cognitive remediation is an area of current interest to target the deficits noted in individuals with schizophrenia; the degree of observed benefit has been mixed.[68, 69] Pharmacological and non-pharmacological interventions directed to the management of MetS and its factors can be better assessed from a functional perspective.[70-72] It has been suggested that targeting other endocrine activity can also provide benefit. For example, administration of leptin could potentially result in improved cognitive performance and also have a role in obesity management.[73-75] Genetic and epigenetic factors can also be explored to predict cognitive responses to antipsychotic treatment.[76]

Table 1: Criteria for MetS as proposed by IDF, NCEP-ATP III, and Harmonised criteria

Criteria*	NCEP-ATP III	IDF	Harmonised
↑ Waist Circumference (cm)	> 102 for ♂, > 88 for ♀	≥ 94 for Europid ♂, ≥ 90 for non-Europid ♂, ≥ 80 for ♀	≥ 94 for Europid ♂, ≥ 90 for non-Europid ♂, ≥ 80 for ♀
↑Trigylcerides (mmol/l)	≥ 1.69	≥ 1.7 or on specific treatment	≥ 1.7 or on specific treatment
↓HDL (mmol/l)	< 1.03 for ♂, < 1.29 for ♀	< 1.03 for ♂, < 1.29 for ♀, or on specific treatment	< 1.0 for ♂, < 1.3 for ♀, or on specific treatment
↑ Blood Pressure (mm Hg)	BP ≥ 130/85	Systolic BP ≥ 130, Diastolic BP ≥ 85, or previously diagnosed HTN	Systolic BP ≥ 130, Diastolic BP ≥ 85, or previously diagnosed HTN
↑ Fasting Plasma Glucose (mmol/l)	≥ 6.1	≥ 5.6, or previously diagnosed Type 2 diabetes	≥ 5.6, or previously diagnosed Type 2 diabetes

*Under the IDF definition, obesity plus any 2 of the remaining 4 criteria must be met for a diagnosis for MetS, while under NCEP-ATP III definition, 3 of out of 5 criteria must be met for the diagnosis. Under the Harmonised criteria (having the same cut-offs as the IDF criteria), meeting any 3 out of the 5 criteria would qualify for a diagnosis of MetS. (*adapted from Sivapalan et al, 2015 – in submission*)

Table 2: Population Demographics

	n = 47	%
Gender		
Male	34	72.3%
Female	13	27.7%
Employment		
Unemployed	23	48.9%
Student	6	12.8%
Employed	17	36.2%
Unknown	1	2.1%
Average years of education = 12.6y		
Medication (by level of metabolic effect)		
Low Effect	15	31.9%
Medium Effect	16	34.0%
High Effect	16	34.0%
Cannabis Use in Past 30 days		
Yes	14	29.8%
No	33	70.2%
Current Tobacco Use		
Yes	20	42.6%
No	27	57.4%
Ethnicity		
Caucasian	23	48.9%
Asian	7	14.9%
Middle Eastern - Mediterranean	6	12.8%
African	4	8.5%
Central & South American	2	4.3%
Indigenous	5	10.6%
Diagnoses		
Schizophrenia	18	38.3%
Substance Induced Psychosis	6	12.8%
Affective Psychosis	11	23.4%
Unspecified Psychosis	10	21.3%
Anxiety	2	4.3%

Table 3: Number of Individuals Meeting Criteria* for MetS and individual Mets parameters

MetS Factor	# abN	% abN	Mean	Range	SD
Meeting Full Criteria	2	4.3%	-	-	
Fasting Blood Glucose	0	0%	4.9 mmol/l	3.9 - 5.8 mmol/l	0.4 mmol/l
HDL Cholesterol	12	25.5%	1.4 mmol/l	0.7 - 2.4 mmol/l	0.3 mmol/l
Triglycerides	13	27.7%	1.3 mmol/l	0.4 - 2.9 mmol/l	0.6 mmol/l
Blood Pressure	11	23.4%	$^{122}/_{70}$ mmHg	$^{99\text{-}145}/_{44\text{-}91}$ mmHg	$^{9.6}/_{10.7}$ mmHg
Waist Circumference	6	12.8%	86.7 cm	63.5 - 111.8 cm	10.1 cm

*Critera as defined by NCEP-ATP III

Table 4: Linear regression analysis outputs of the most significant relationships between fasting serum glucose levels and specific cognitive assessments from the MCCB

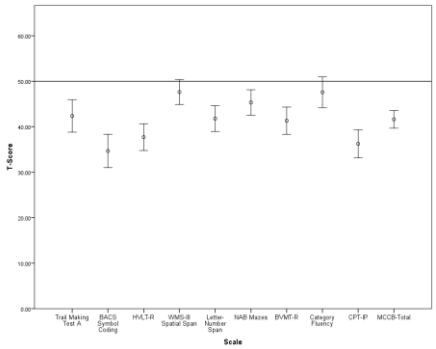
Cognitive Assessment	Factor	β	*t*-score	*p*-value
MCCB-Total	*Glucose*	0.29	2.11	0.04
	Medication	-0.17	-1.22	0.23
	*Occupation**	-0.20	-1.36	0.18
	*Education***	0.14	0.90	0.37
	*Exposure****	-0.21	-1.55	0.13
WMS III-Spatial Span	*Glucose*	0.33	2.36	0.02
	Medication	-0.13	-0.94	0.35
BVMT-R	*Glucose*	0.30	2.15	0.04
	Medication	-0.17	-1.22	0.23
NAB Mazes	*Glucose*	0.34	2.41	0.02

*Occupational Status

**Years of education

***Duration of antipsychotic medication exposure prior to assessment

Figure 1: Cognitive Profile of Population* (Average scores presented as T-Scores)



*Average and range of T-Scores obtained by the assessed sample of individuals at EEPIC in each of the cognitive assessments of the MCCB. The line at the T-Score of 50 represents the average of the general population.

Acknowledgements

We would like to acknowledge the assistance of Ms. Majeau and Ms. Bolt in the collection of the data. We would also like to acknowledge the support of the University of Alberta Department of Psychology Industrial Internship Program. Dr. Sivapalan would like to acknowledge the support of Dr. R. Lodhi in providing an introduction to statistical analysis using SPSS.

Contributions

Dr. Sivapalan conducted the analysis of the data presented and was the primary author of the manuscript. The neuropsychological assessment was carried out under the supervision of Dr. Purdon and Dr. Newton through the clinical services at Alberta Hospital Edmonton Neuropsychology Department. Dr. Aitchison and Dr. Purdon provided significant review and feedback regarding the manuscript.

Funding

Dr. Sivapalan received support from the University of Alberta, Department of Psychiatry to conduct a M.Sc. in Psychiatry at the University of Alberta, and from Alberta Health Services as a Resident Physician. Dr. Aitchison holds an Alberta Centennial Addiction and Mental Health Research Chair, funded by the Government of Alberta. Dr. Purdon and Dr. Newton are supported by Alberta Health Services Addictions and Mental Health – Edmonton Zone. Funding for this study was provided, in part, by the Bebensee Schizophrenia Research Unit.

References

1. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002; 106: 3143-421.

2. Alberti KG, Zimmet P and Shaw J. The metabolic syndrome--a new worldwide definition. *Lancet*. 2005; 366: 1059-62.

3. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009; 120: 1640-5.

4. Zimmet P, Alberti KG, Kaufman F, et al. The metabolic syndrome in children and adolescents - an IDF consensus report. *Pediatr. Diabetes*. 2007; 8: 299-306.

5. De Hert M, van Winkel R, Van Eyck D, et al. Prevalence of diabetes, metabolic syndrome and metabolic abnormalities in schizophrenia over the course of the illness: a cross-sectional study. *Clin. Pract. Epidemiol. Ment. Health*. 2006; 2: 14.

6. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W and De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. *Schizophr. Bull*. 2013; 39: 306-18.

7. Vancampfort D, Wampers M, Mitchell AJ, et al. A meta-analysis of cardio-metabolic abnormalities in drug naive, first-episode and multi-episode patients with schizophrenia versus general population controls. *World Psychiatry.* 2013; 12: 240-50.

8. Papanastasiou E. The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. *Ther. Adv. Psychopharmacol*. 2013; 3: 33-51.

9. Yates KF, Sweat V, Yau PL, Turchiano MM and Convit A. Impact of metabolic syndrome on cognition and brain: a selected review of the literature. *Arterioscl. Throm. Vas*. 2012; 32: 2060-7.

10. Elias MF, Elias PK, Sullivan LM, Wolf PA and D'Agostino RB. Obesity, diabetes and cognitive deficit: The Framingham Heart Study. *Neurobiol. Aging*. 2005; 26 Suppl 1: 11-6.

11. Pavlik VN, Hyman DJ and Doody R. Cardiovascular risk factors and cognitive function in adults 30-59 years of age (NHANES III). *Neuroepidemiology*. 2005; 24: 42-50.

12. Taylor VH and MacQueen GM. Cognitive dysfunction associated with metabolic syndrome. *Obes. Rev*. 2007; 8: 409-18.

13. Gatto NM, Henderson VW, St John JA, McCleary C, Hodis HN and Mack WJ. Metabolic syndrome and cognitive function in healthy middle-aged and older adults without diabetes. *Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn*. 2008; 15: 627-41.

14. Segura B, Jurado MA, Freixenet N, Albuin C, Muniesa J and Junque C. Mental slowness and executive dysfunctions in patients with metabolic syndrome. *Neurosci. Lett*. 2009; 462: 49-53.

15. van den Berg E, Kloppenborg RP, Kessels RP, Kappelle LJ and Biessels GJ. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. *Biochim. Biophys. Acta*. 2009; 1792: 470-81.

16. Troisi A. Cholesterol in coronary heart disease and psychiatric disorders: same or opposite effects on morbidity risk? *Neurosci. Biobehav. R*. 2009; 33: 125-32.

17. Hassenstab JJ, Sweat V, Bruehl H and Convit A. Metabolic syndrome is associated with learning and recall impairment in middle age. *Dement. Geritr. Cogn*. 2010; 29: 356-62.

18. Tournoy J, Lee DM, Pendleton N, et al. Association of cognitive performance with the metabolic syndrome and with glycaemia in middle-aged and older European men: the European Male Ageing Study. *Diabetes Metab. Res. Rev*. 2010; 26: 668-76.

19. Vieira JR, Elkind MS, Moon YP, et al. The metabolic syndrome and cognitive performance: the Northern Manhattan Study. *Neuroepidemiology*. 2011; 37: 153-9.

20. Yau PL, Castro MG, Tagani A, Tsui WH and Convit A. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. *Pediatrics*. 2012; 130: e856-64.

21. Wolf PA, Beiser A, Elias MF, Au R, Vasan RS and Seshadri S. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. *Curr. Alzheimer Res*. 2007; 4: 111-6.

22. Liang J, Matheson BE, Kaye WH and Boutelle KN. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. *Int. J. Obes. (Lond)*. 2014; 38: 494-506.

23. Gluck ME, Ziker C, Schwegler M, Thearle M, Votruba SB and Krakoff J. Impaired glucose regulation is associated with poorer performance on the Stroop Task. *Physiol. Behav*. 2013; 122: 113-9.

24. Meikle A, Riby LM and Stollery B. The impact of glucose ingestion and gluco-regulatory control on cognitive performance: a comparison of younger and middle aged adults. *Hum. Psychopharmacol*. 2004; 19: 523-35.

25. Smith MA, Riby LM, Eekelen JA and Foster JK. Glucose enhancement of human memory: a comprehensive research review of the glucose memory facilitation effect. *Neurosci. Biobehav. R*. 2011; 35: 770-83.

26. Owen L, Scholey A, Finnegan Y and Sunram-Lea SI. Response variability to glucose facilitation of cognitive enhancement. *Brit. J. Nutr*. 2013; 110: 1873-84.

27. Bilder RM, Goldman RS, Robinson D, et al. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *Am. J. Psychiatry*. 2000; 157: 549-59.

28. Addington J, Brooks BL and Addington D. Cognitive functioning in first episode psychosis: initial presentation. *Schizophr. Res.*. 2003; 62: 59-64.

29. Fitzgerald D, Lucas S, Redoblado MA, et al. Cognitive functioning in young people with first episode psychosis: relationship to diagnosis and clinical characteristics. *Aust. N. Z. J. Psychiatry*. 2004; 38: 501-10.

30. Hill SK, Keshavan MS, Thase ME and Sweeney JA. Neuropsychological dysfunction in antipsychotic-naive first-episode unipolar psychotic depression. *Am. J. Psychiatry*. 2004; 161: 996-1003.

31. Bora E. Developmental trajectory of cognitive impairment in bipolar disorder: comparison with schizophrenia. *Eur Neuropsychopharmacol*. 2015; 25: 158-68.

32. Friedman JI, Wallenstein S, Moshier E, et al. The effects of hypertension and body mass index on cognition in schizophrenia. *Am. J. Psychiatry.* 2010; 167: 1232-9.

33. Lindenmayer JP, Khan A, Kaushik S, et al. Relationship between metabolic syndrome and cognition in patients with schizophrenia. *Schizophr. Res.*. 2012; 142: 171-6.

34. Li C, Zhan G, Rao S and Zhang H. Metabolic syndrome and its factors affect cognitive function in chronic schizophrenia complicated by metabolic syndrome. *J. Nerv. Ment. Dis*. 2014; 202: 313-8.

35. De Nijs J and Pet MA. Metabolic syndrome in patients with schizophrenia is associated with poor cognitive performance and poor premorbid school performance. *Eur. Neuropsychopharm*. 2014; 24: S485-S6.

36. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am. J. Psychiatry*. 2008; 165: 203-13.

37. Kern RS, Nuechterlein KH, Green MF, et al. The MATRICS Consensus Cognitive Battery, part 2: co-norming and standardization. *Am. J. Psychiatry*. 2008; 165: 214-20.

38. August SM, Kiwanuka JN, McMahon RP and Gold JM. The MATRICS Consensus Cognitive Battery (MCCB): clinical and cognitive correlates. *Schizophr. Res.*. 2012; 134: 76-82.

39. Spreen O. A compendium of neuropsychological tests : administration, norms, and commentary. In: Strauss E, (ed.). 2nd ed. ed. New York :: Oxford University Press, 1998.

40. Snyder PJ, Jackson CE, Piskulic D, Olver J, Norman T and Maruff P. Spatial working memory and problem solving in schizophrenia: the effect of symptom stabilization with atypical antipsychotic medication. *Psychiat. Res*. 2008; 160: 316-26.

41. Rabin RA, Zakzanis KK and George TP. The effects of cannabis use on neurocognition in schizophrenia: a meta-analysis. *Schizophr. Res*. 2011; 128: 111-6.

42. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005; 19 Suppl 1: 1-93.

43. Hasnain M, Fredrickson SK, Vieweg WV and Pandurangi AK. Metabolic syndrome associated with schizophrenia and atypical antipsychotics. *Curr. Diab. Rep*. 2010; 10: 209-16.

44. Benjamini Y and Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J. Roy. Stat. Soc. B Met*. 1995; 57: 289-300.

45. Attux C, Quintana MI and Chaves AC. Weight gain, dyslipidemia and altered parameters for metabolic syndrome on first episode psychotic patients after six-month follow-up. *Rev. Bras. Psiquiatr*. 2007; 29: 346-9.

46. Srihari VH, Phutane VH, Ozkan B, et al. Cardiovascular mortality in schizophrenia: defining a critical period for prevention. *Schizophr. Res.*. 2013; 146: 64-8.

47. Correll CU, Robinson DG, Schooler NR, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry*. 2014; 71: 1350-63.

48. Rao DP, Dai S, Lagace C and Krewski D. Metabolic syndrome and chronic disease. *Chronic Dis. Inj. Can*. 2014; 34: 36-45.

49. Foley DL and Morley KI. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. *Arch. Gen. Psychiat*. 2011; 68: 609-16.

50. Heinrichs RW and Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*. 1998; 12: 426-45.

51. Keefe RS, Bilder RM, Harvey PD, et al. Baseline neurocognitive deficits in the CATIE schizophrenia trial. *Neuropsychopharmacol*. 2006; 31: 2033-46.

52. Kern RS, Gold JM, Dickinson D, et al. The MCCB impairment profile for schizophrenia outpatients: results from the MATRICS psychometric and standardization study. *Schizophr. Res.*. 2011; 126: 124-31.

53. McCleery A, Ventura J, Kern RS, et al. Cognitive functioning in first-episode schizophrenia: MATRICS Consensus Cognitive Battery (MCCB) Profile of Impairment. *Schizophr. Res*. 2014; 157: 33-9.

54. Bellino S, Rocca P, Patria L, et al. Relationships of age at onset with clinical features and cognitive functions in a sample of schizophrenia patients. *J. Clin. Psychiatry*. 2004; 65: 908-14.

55. Rajji TK, Ismail Z and Mulsant BH. Age at onset and cognition in schizophrenia: meta-analysis. *Br. J. Psychiatry*. 2009; 195: 286-93.

56. Caravaggio F, Hahn M, Nakajima S, Gerretsen P, Remington G and Graff-Guerrero A. Reduced insulin-receptor mediated modulation of striatal dopamine release by basal insulin as a possible contributing factor to hyperdopaminergia in schizophrenia. *Med. Hypotheses*. 2015; 85: 391-6.

57. Greenwood CE and Winocur G. High-fat diets, insulin resistance and declining cognitive function. *Neurobiol. Aging*. 2005; 26 Suppl 1: 42-5.

58. Wendt PE and Risberg J. Cortical activation during visual spatial processing: relation between hemispheric asymmetry of blood flow and performance. *Brain Cogn*. 1994; 24: 87-103.

59. Heckers S, Goff D and Weiss AP. Reversed hemispheric asymmetry during simple visual perception in schizophrenia. *Psychiat. Res*. 2002; 116: 25-32.

60. Gur RE, Skolnick BE, Gur RC, et al. Brain function in psychiatric disorders. I. Regional cerebral blood flow in medicated schizophrenics. *Arch. Gen. Psychiat*. 1983; 40: 1250-4.

61. Gruzelier JH. Functional neuropsychophysiological asymmetry in schizophrenia: a review and reorientation. *Schizophr. Bull*. 1999; 25: 91-120.

62. Gur RE, Gur RC, Skolnick BE, et al. Brain function in psychiatric disorders. III. Regional cerebral blood flow in unmedicated schizophrenics. *Arch. Gen. Psychiat*. 1985; 42: 329-34.

63. Schulingkamp RJ, Pagano TC, Hung D and Raffa RB. Insulin receptors and insulin action in the brain: review and clinical implications. *Neurosci. Biobehav. R*. 2000; 24: 855-72.

64. Saddichha S, Ameen S and Akhtar S. Incidence of new onset metabolic syndrome with atypical antipsychotics in first episode schizophrenia: a six-week prospective study in Indian female patients. *Schizophr. Res.*. 2007; 95: 247.

65. Bak M, Fransen A, Janssen J, van Os J and Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. *PLOS ONE.* 2014; 9: e94112.

66. Gonzalez-Blanch C, Crespo-Facorro B, Alvarez-Jimenez M, et al. Lack of association between clinical and cognitive change in first-episode psychosis: the first 6 weeks of treatment. *Can. J. Psychiatry*. 2008; 53: 839-47.

67. Keefe RS. The contribution of neuropsychology to psychiatry. *Am. J. Psychiatry*. 1995; 152: 6-15.

68. Barlati S, Deste G, De Peri L, Ariu C and Vita A. Cognitive remediation in schizophrenia: current status and future perspectives. *Schizophr. Res. Treatment*. 2013; 2013: 156084.

69. Zaytseva Y, Korsakova N, Agius M and Gurovich I. Neurocognitive functioning in schizophrenia and during the early phases of psychosis: targeting cognitive remediation interventions. *Biomed. Res. Int*. 2013; 2013: 819587.

70. Wardle J, Rogers P, Judd P, et al. Randomized trial of the effects of cholesterol-lowering dietary treatment on psychological function. *Am. J. Med*. 2000; 108: 547-53.

71. Bergqvist A, Karlsson M, Foldemo A, Wardig R and Hultsjo S. Preventing the development of metabolic syndrome in people with psychotic disorders--difficult, but possible: experiences of staff working in psychosis outpatient care in Sweden. *Issues Ment. Health N*. 2013; 34: 350-8.

72. Vincenzi B, Stock S, Borba CP, et al. A randomized placebo-controlled pilot study of pravastatin as an adjunctive therapy in schizophrenia patients: effect on inflammation, psychopathology, cognition and lipid metabolism. *Schizophr. Res*. 2014; 159: 395-403.

73. Harvey J. Leptin regulation of neuronal excitability and cognitive function. *Curr. Opin. Pharmacol*. 2007; 7: 643-7.

74. Harvey J, Shanley LJ, O'Malley D and Irving AJ. Leptin: a potential cognitive enhancer? *Biochem. Soc. T*. 2005; 33: 1029-32.

75. Friedman J. The long road to leptin. *J. Clin. Invest*. 2016; 126: 4727-34.

76. Weickert TW, Goldberg TE, Mishara A, et al. Catechol-O-methyltransferase val108/158met genotype predicts working memory response to antipsychotic medications. *Biol. Psychiat.*. 2004; 56: 677-82.

5. Further discussion: considering the roles of other parameters of MetS

The second paper makes the suggestion that for certain right-sided cognitive domains, having a slightly higher blood glucose level may be of benefit when engaged in these mental tasks. There may be a number of mechanisms at play, including the idea of differential cerebral blood flows and looking at how the human brain may compensate for this differential. It should still be reinforced that this finding may represent part of an upside-down "U" relationship between insulin resistance and cognitive functioning. That would be in keeping with the previous findings noted in the first paper, where a diagnosis of diabetes was associated with cognitive impairments in processing speed, attention, and memory. A larger population with a wider range of values would be helpful to better characterise this interesting relationship.

With respect to obesity, a few other ideas may be worth considering, not explored in the second paper. One analysis looking at obesity, co-morbid somatic disorders, and cognitive functioning seemed to indicate that increased age in individuals with obesity is associated with both increased somatic co-morbidities and to decreased cognitive performance (Kiunke et al., 2013). Our population, due to the nature of the intake criteria of the clinical service, represent a somewhat narrow age group. A study of otherwise healthy children and adolescents did not find an association between elevated BMI and neuropsychological performance; however, it was also noted that performance in otherwise healthy adults was impaired (Gunstad et al., 2006; Gunstad et al., 2007; Gunstad et al., 2008). The prior studies limited their assessments to verbal memory, attention, and tasks of executive functioning (including the Austin Maze, Stroop, and the Trail Making Test-B), and found impairments in two of the three tasks of executive functioning, but not attention. Overall, these studies appear to suggest that the

effects of obesity on cognitive functioning may be due to more of a chronic process, rather than to an acute presentation. Owing to the various mechanisms through which adipose cells can exert an influence on the brain and its functioning (e.g. Chapter 3, Figure 4), it can be appreciated that evolution of any impairment may take time.

Perhaps the most relevant study to our population is one that included a large number of Chinese patients (n = 896) with schizophrenia or schizophreniform disorder. Obese subjects demonstrated more impairment on the Trail Making Test: Part B, Wechsler Memory Scale - Revised Reproduction Test, and the Wechsler Adult Intelligence Scale Digit Symbol Test. This finding is in line with one of our original hypotheses that obesity would be associated with impairments in visuospatial tasks, attention, and working memory (Guo et al., 2013).

In a *post hoc* analysis of the data pertaining to the subjects presenting to EEPIC, several trends involving other biomarkers of MetS were noted, however, the significance of these results remain unclear. Notably higher systolic blood pressures and worsening serum triglyceride levels showed trend associations with impairments in verbal learning (r = -0.27, p = 0.07; r = -0.29, p = 0.05, respectively). As well, increased levels of serum HDL cholesterol approached a trend level association with higher scores in a task of processing speed (r = 0.37, p = 0.01). In all of these findings, the respective biomarker of MetS was treated as a continuous variable, and so while these trends may suggest some degree of cognitive dysfunction with worsening metabolic parameters, it is not specifically clear that it is with abnormal values that the dysfunction occurs. The significance of these relationships was lost once correction was applied

for multiple testing, but may suggest areas for further study with larger sample sizes. These relationships have been described previously but inconsistently.

One 2008 study demonstrated that hypertension was associated with verbal learning impairments, but also showed an association with semantic memory (Gatto et al., 2008). This was supported in a later, 2014 study, which also showed negative associations of HTN with executive functioning and psychomotor performance (Levin et al., 2014). It should be noted that Taylor and MacQueen (2007) found HTN to be associated with impairments in most cognitive domains, describing a mechanism that was consistent with chronic presentations and involving the presence of white matter lesions. This would not likely be the case in a population of older adolescents and young adults having FEP, and it is difficult to ascertain which cognitive domain is affected first, if any. Another 2008 study of 121 African-American adults did not support the finding that HTN was associated with verbal learning impairment (Sims et al., 2008). Lastly, a factor analysis looking at a non-geriatric population of individuals with schizophrenia in fact describes cognitive benefits associated with HTN, and infers that improved cerebral circulation may play a role in this finding (Wysokiński et al., 2013). The generally broad results make it difficult to draw any specific inferences with respect to the relationships between HTN and specific cognitive domains.

With respect to the association between elevated triglycerides and verbal learning, at least two previous studies appear to support this finding, but the recent factor analysis mentioned above did not report on any cognitive deficits associated with elevated serum triglycerides, while reporting a number of deficits associated with elevated low-density serum lipoprotein levels

(Farr et al., 2008; Sims et al., 2008; Wysokiński et al., 2013). Elevated triglycerides have also been associated with dysfunction in other domains such as attention and some aspects of executive functioning (Boyer et al., 2013; Lindenmayer et al., 2012). With respect to the finding of HDL cholesterol associated with improved processing speed, previous studies that have also reported an improvement in cognitive performance with higher level of HDL cholesterol; however, this effect has mainly been noted in older geriatric populations, and mostly amongst women (Chanti-Ketterl et al., 2015; Crichton et al., 2014; Hottman et al., 2014; Lv et al., 2016). Given the broadness of reported benefits compared to fairly circumscribed findings in the current report, it seems more likely that this finding is a false positive; further research with a larger FEP population will be required. It has also been suggested that lipid levels that are too low may also be associated with cognitive deficits, suggesting that similar to the relationship with glucose, that there may be a U-shaped relationship between cognitive performance and serum lipid levels; the direction of the "U" may depend on which type of lipid is being considered.

The variability in the literature described above may reflect the idea that unlike obesity and insulin resistance, which are arguably the more serious parameters of MetS, HTN and dyslipidemia may have a role where abnormalities in these parameters simply contribute additive effects with respect to cognitive dysfunction to individuals who are already obese or have insulin resistance. More research looking at the relationships between cognitive functioning and the metabolic parameters of blood pressure and serum lipid profiles in individuals with SMI are warranted.

6. Conclusions

This area of research is an active one at this time as it focuses on early interventions to reduce overall long-term morbidity and mortality of SMI and its associated disorders including MetS. MetS is a common comorbidity amongst individuals with SMI, and when an individual has both MetS and SMI, other aspects of their wellbeing and functioning are affected (e.g., cognition). Individuals with SMI already appear to have a certain amount of cognitive dysfunction at baseline, and the literature review suggests that when MetS is part of the presentation, the patient appears to suffer from a greater degree of cognitive impairment. In general, the consensus amongst most studies is that the greater the number of abnormal MetS parameters that an individual has, the greater the cognitive impairment. However, there does appear to be some suggestion that having slightly abnormal values in a specific parameter (e.g. serum cholesterol, blood pressure, measures of insulin resistance) may offer some cognitive benefit. The study described in Chapter 4 is one such example, where serum glucose values at the higher end of the normal range appear to confer some cognitive benefit in a series of assessments that related to non-verbal cognitive functions. This appears to be a unique finding at this time, and it is hopeful that further study with a larger number of subjects will allow for better analysis. If this result were to hold up, one could consider continuing with a functional neuroimaging study to better investigate a possible mechanism for this finding. Results such as this have the potential to modify clinical care strategies in the near future.

Complete List of References

2002. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 106(25), 3143-3421.

2006. Handbook of functional neuroimaging of cognition, in: Cabeza, R., Kingstone, A. (Eds.), 2nd ed. ed. MIT Press, Cambridge, Mass.

2013. Diagnostic and statistical manual of mental disorders : DSM-5, 5th ed. ed. American Psychiatric Publishing, Washington, D.C.

Addington, J., Brooks, B.L., Addington, D., 2003. Cognitive functioning in first episode psychosis: initial presentation. Schizophr. Res. 62(1-2), 59-64.

Alberti, K.G., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., Fruchart, J.C., James, W.P., Loria, C.M., Smith, S.C., Jr., International Diabetes Federation Task Force on, E., Prevention, Hational Heart, L., Blood, I., American Heart, A., World Heart, F., International Atherosclerosis, S., International Association for the Study of, O., 2009. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 120(16), 1640-1645.

Alberti, K.G., Zimmet, P., Shaw, J., 2005. The metabolic syndrome--a new worldwide definition. Lancet. 366(9491), 1059-1062.

Alberti, K.G., Zimmet, P.Z., 1998. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabetic Med. 15(7), 539-553.

Altshuler, L.L., Ventura, J., van Gorp, W.G., Green, M.F., Theberge, D.C., Mintz, J., 2004. Neurocognitive function in clinically stable men with bipolar I disorder or schizophrenia and normal control subjects. Biol. Psychiat. 56(8), 560-569.

American Diabetes Association, 2004. Consensus development conference on antipsychotic drugs and obesity and diabetes. J. Clin. Psychiatry. 65(2), 267-272.

Ardila, A., Montanes, P., Gempeler, J., 1986. Echoic memory and language perception. Brain Lang. 29(1), 134-140.

Attux, C., Quintana, M.I., Chaves, A.C., 2007. Weight gain, dyslipidemia and altered parameters for metabolic syndrome on first episode psychotic patients after six-month follow-up. Rev. Bras. Psiquiatr. 29(4), 346-349.

August, S.M., Kiwanuka, J.N., McMahon, R.P., Gold, J.M., 2012. The MATRICS Consensus Cognitive Battery (MCCB): clinical and cognitive correlates. Schizophr. Res. 134(1), 76-82.

Awh, E., Vogel, E.K., Oh, S.H., 2006. Interactions between attention and working memory. Neuroscience. 139(1), 201-208.

Bak, M., Fransen, A., Janssen, J., van Os, J., Drukker, M., 2014. Almost all antipsychotics result in weight gain: a meta-analysis. PLOS ONE. 9(4), e94112.

Balhara, Y.P.S., 2011. Diabetes and psychiatric disorders. Indian. J. Endocr. Metab. 15(4), 274-283.

Barlati, S., Deste, G., De Peri, L., Ariu, C., Vita, A., 2013. Cognitive remediation in schizophrenia: current status and future perspectives. Schizophr. Res. Treatment. 2013, 156084.

Bartoli, F., Carra, G., Crocamo, C., Carretta, D., Clerici, M., 2013. Bipolar disorder, schizophrenia, and metabolic syndrome. Am. J. Psychiatry. 170(8), 927-928.

Beck, L.H., Bransome, E.D., Jr., Mirsky, A.F., Rosvold, H.E., Sarason, I., 1956. A continuous performance test of brain damage. J. Consult. Psychol. 20(5), 343-350.

Bellino, S., Rocca, P., Patria, L., Marchiaro, L., Rasetti, R., Di Lorenzo, R., Paradiso, E., Bogetto, F., 2004. Relationships of age at onset with clinical features and cognitive functions in a sample of schizophrenia patients. J. Clin. Psychiatry. 65(7), 908-914.

Benedict, R.H.B., 1997. Brief Visuospatial Memory test - Revised: Professional Manual. Psychological Assesment Resources, Inc., Lutz, Florida, USA.

Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. J. Roy. Stat. Soc. B Met. 57(1), 289-300.

Bergqvist, A., Karlsson, M., Foldemo, A., Wardig, R., Hultsjo, S., 2013. Preventing the development of metabolic syndrome in people with psychotic disorders--difficult, but possible: experiences of staff working in psychosis outpatient care in Sweden. Issues Ment. Health N. 34(5), 350-358.

Bilder, R.M., Goldman, R.S., Robinson, D., Reiter, G., Bell, L., Bates, J.A., Pappadopulos, E., Willson, D.F., Alvir, J.M., Woerner, M.G., Geisler, S., Kane, J.M., Lieberman, J.A., 2000. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. Am. J. Psychiatry. 157(4), 549-559.

Binder, J.R., Desai, R.H., 2011. The neurobiology of semantic memory. Trends Cogn. Sci. 15(11), 527-536.

Bora, E., 2015. Developmental trajectory of cognitive impairment in bipolar disorder: comparison with schizophrenia. Eur. Neuropsychopharmacol.25(2), 158-168.

Bora, E., Pantelis, C., 2015. Meta-analysis of Cognitive Impairment in First-Episode Bipolar Disorder: Comparison With First-Episode Schizophrenia and Healthy Controls. Schizophr. Bull. 41(5), 1095-1104.

Boyer, L., Richieri, R., Dassa, D., Boucekine, M., Fernandez, J., Vaillant, F., Padovani, R., Auquier, P., Lancon, C., 2013. Association of metabolic syndrome and inflammation with neurocognition in patients with schizophrenia. Psychiat. Res. 210(2), 381-386.

Brandt, J., Benedict, R.H.B., 2001. Hopkins verbal learning test - Revised. Administration Manual. Psychological Assessment Resources, Inc., Lutz, Florida, USA.

Bressington, D.T., Mui, J., Cheung, E.F., Petch, J., Clark, A.B., Gray, R., 2013. The prevalence of metabolic syndrome amongst patients with severe mental illness in the community in Hong Kong--a cross sectional study. BMC Psychiatry. 13, 87.

Brown, J., 1964. Short-Term Memory. Br. Med. Bull. 20, 8-11.

Bugra, H., Studerus, E., Rapp, C., Tamagni, C., Aston, J., Borgwardt, S., Riecher-Rossler, A., 2013. Cannabis use and cognitive functions in at-risk mental state and first episode psychosis. Psychopharmacology (Berl). 230(2), 299-308.

Burgess, P.W., Alderman, N., Evans, J., Emslie, H., Wilson, B.A., 1998. The ecological validity of tests of executive function. J. Int. Neuropsych. Soc. 4(6), 547-558.

Cabeza, R., Nyberg, L., 2000. Imaging cognition II: An empirical review of 275 PET and fMRI studies. J. Cogn. Neurosci. 12(1), 1-47.

Caeyenberghs, K., Leemans, A., 2014. Hemispheric lateralization of topological organization in structural brain networks. Hum. Brain Mapp. 35(9), 4944-4957.

Caravaggio, F., Hahn, M., Nakajima, S., Gerretsen, P., Remington, G., Graff-Guerrero, A., 2015. Reduced insulin-receptor mediated modulation of striatal dopamine release by basal insulin as a possible contributing factor to hyperdopaminergia in schizophrenia. Med. Hypotheses. 85(4), 391-396.

Castillo, R.I., Rojo, L.E., Henriquez-Henriquez, M., Silva, H., Maturana, A., Villar, M.J., Fuentes, M., Gaspar, P.A., 2016. From Molecules to the Clinic: Linking Schizophrenia and Metabolic Syndrome through Sphingolipids Metabolism. Front. Neurosci-Switz. 10, 488.

Chanti-Ketterl, M., Andel, R., Lerch, O., Laczo, J., Hort, J., 2015. Cholesterol and cognitive performance among community volunteers from the Czech Republic. Int. Psychogeriatr. 27(12), 2087-2095.

Chevalier, N., Kurth, S., Doucette, M.R., Wiseheart, M., Deoni, S.C., Dean, D.C., 3rd, O'Muircheartaigh, J., Blackwell, K.A., Munakata, Y., LeBourgeois, M.K., 2015. Myelination Is Associated with Processing Speed in Early Childhood: Preliminary Insights. PLOS ONE. 10(10), e0139897.

Cohn, T., Prud'homme, D., Streiner, D., Kameh, H., Remington, G., 2004. Characterizing coronary heart disease risk in chronic schizophrenia: high prevalence of the metabolic syndrome. Can. J. Psychiatry. 49(11), 753-760.

Convit, A., 2005. Links between cognitive impairment in insulin resistance: an explanatory model. Neurobiol. Aging. 26 Suppl 1, 31-35.

Corballis, P.M., 2003. Visuospatial processing and the right-hemisphere interpreter. Brain Cogn. 53(2), 171-176.

Corballis, P.M., Funnell, M.G., Gazzaniga, M.S., 1999. A dissociation between spatial and identity matching in callosotomy patients. Neuroreport. 10(10), 2183-2187.

Corballis, P.M., Funnell, M.G., Gazzaniga, M.S., 2002. Hemispheric asymmetries for simple visual judgments in the split brain. Neuropsychologia. 40(4), 401-410.

Corbetta, M., Kincade, J.M., Ollinger, J.M., McAvoy, M.P., Shulman, G.L., 2000. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat. Neurosci. 3(3), 292-297.

Corigliano, V., De Carolis, A., Trovini, G., Dehning, J., Di Pietro, S., Curto, M., Donato, N., De Pisa, E., Girardi, P., Comparelli, A., 2014. Neurocognition in schizophrenia: from prodrome to multi-episode illness. Psychiat. Res. 220(1-2), 129-134.

Cornblatt, B.A., Risch, N.J., Faris, G., Friedman, D., Erlenmeyer-Kimling, L., 1988. The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. Psychiat. Res. 26(2), 223-238.

Correll, C.U., Detraux, J., De Lepeleire, J., De Hert, M., 2015. Effects of antipsychotics, antidepressants and mood stabilizers on risk for physical diseases in people with schizophrenia, depression and bipolar disorder. World Psychiatry. 14(2), 119-136.

Correll, C.U., Robinson, D.G., Schooler, N.R., Brunette, M.F., Mueser, K.T., Rosenheck, R.A., Marcy, P., Addington, J., Estroff, S.E., Robinson, J., Penn, D.L., Azrin, S., Goldstein, A., Severe, J., Heinssen, R., Kane, J.M., 2014. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. JAMA Psychiatry. 71(12), 1350-1363.

Crichton, G.E., Elias, M.F., Buckley, J.D., Murphy, K.J., Bryan, J., Frisardi, V., 2012. Metabolic syndrome, cognitive performance, and dementia. J. Alzheimers Dis. 30 Suppl 2, S77-87.

Crichton, G.E., Elias, M.F., Davey, A., Sullivan, K.J., Robbins, M.A., 2014. Higher HDL cholesterol is associated with better cognitive function: the Maine-Syracuse study. J. Int. Neuropsych. Soc. 20(10), 961-970.

Crosson, B., Rao, S.M., Woodley, S.J., Rosen, A.C., Bobholz, J.A., Mayer, A., Cunningham, J.M., Hammeke, T.A., Fuller, S.A., Binder, J.R., Cox, R.W., Stein, E.A., 1999. Mapping of semantic, phonological, and orthographic verbal working memory in normal adults with functional magnetic resonance imaging. Neuropsychology. 13(2), 171-187.

Cunha, P.J., Rosa, P.G., Ayres Ade, M., Duran, F.L., Santos, L.C., Scazufca, M., Menezes, P.R., dos Santos, B., Murray, R.M., Crippa, J.A., Busatto, G.F., Schaufelberger, M.S., 2013. Cannabis use, cognition and brain structure in first-episode psychosis. Schizophr. Res. 147(2-3), 209-215.

Davidson, M., Galderisi, S., Weiser, M., Werbeloff, N., Fleischhacker, W.W., Keefe, R.S., Boter, H., Keet, I.P., Prelipceanu, D., Rybakowski, J.K., Libiger, J., Hummer, M., Dollfus, S., Lopez-Ibor, J.J., Hranov, L.G., Gaebel, W., Peuskens, J., Lindefors, N., Riecher-Rossler, A., Kahn, R.S., 2009. Cognitive effects of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: a randomized, open-label clinical trial (EUFEST). Am. J. Psychiatry. 166(6), 675-682.

De Hert , M., Correll, C.U., Bobes, J., Cetkovich-Bakmas, M., Cohen, D., Asai, I., Detraux, J., Gautam, S., Moller, H.J., Ndetei, D.M., Newcomer, J.W., Uwakwe, R., Leucht, S., 2011. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. World Psychiatry. 10(1), 52-77.

De Hert, M., van Winkel, R., Van Eyck, D., Hanssens, L., Wampers, M., Scheen, A., Peuskens, J., 2006. Prevalence of diabetes, metabolic syndrome and metabolic abnormalities in schizophrenia over the course of the illness: a cross-sectional study. Clin. Pract. Epidemiol. Ment. Health 2, 14.

De Nijs, J., Pet, M.A., 2014. Metabolic syndrome in patients with schizophrenia is associated with poor cognitive performance and poor premorbid school performance. Eur. Neuropsychopharm. 24, S485-S486.

Di Lollo, V., 1977. Temporal characteristics of iconic memory. Nature. 267(5608), 241-243.

Dickerson, F.B., Stallings, C., Origoni, A., Boronow, J.J., Sullens, A., Yolken, R., 2007. The association between cognitive functioning and occupational status in persons with a recent onset of psychosis. J. Nerv. Ment. Dis. 195(7), 566-571.

Dickinson, D., Harvey, P.D., 2009. Systemic hypotheses for generalized cognitive deficits in schizophrenia: a new take on an old problem. Schizophr. Bull. 35(2), 403-414.

Donoghue, K., Mazzoncini, R., Hart, J., Zanelli, J., Morgan, C., Dazzan, P., Morgan, K.D., Murray, R.M., Jones, P.B., Doody, G.A., 2012. The differential effect of illicit drug use on cognitive function in first-episode psychosis and healthy controls. Acta. Psychiatr. Scand. 125(5), 400-411.

Dubuc, B., 2002. Memory and Learning, The Brain from Top to Bottom. Montreal, Quebec, Canada.

Eckel, R.H., Alberti, K.G., Grundy, S.M., Zimmet, P.Z., 2010. The metabolic syndrome. Lancet. 375(9710), 181-183.

Elias, M.F., Elias, P.K., Sullivan, L.M., Wolf, P.A., D'Agostino, R.B., 2003. Lower cognitive function in the presence of obesity and hypertension: the Framingham heart study. Int. J. Obes. Relat. Metab. Disord. 27(2), 260-268.

Elias, M.F., Elias, P.K., Sullivan, L.M., Wolf, P.A., D'Agostino, R.B., 2005. Obesity, diabetes and cognitive deficit: The Framingham Heart Study. Neurobiol. Aging. 26 Suppl 1, 11-16.

Elias, P.K., Elias, M.F., D'Agostino, R.B., Cupples, L.A., Wilson, P.W., Silbershatz, H., Wolf, P.A., 1997. NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. Diabetes Care. 20(9), 1388-1395.

Ellison-Wright, I., Bullmore, E., 2010. Anatomy of bipolar disorder and schizophrenia: a meta-analysis. Schizophr. Res. 117(1), 1-12.

Eriksson, J., Vogel, E.K., Lansner, A., Bergstrom, F., Nyberg, L., 2015. Neurocognitive Architecture of Working Memory. Neuron. 88(1), 33-46.

Farmer, M.E., Kittner, S.J., Rae, D.S., Bartko, J.J., Regier, D.A., 1995. Education and change in cognitive function. The Epidemiologic Catchment Area Study. Ann. Epidemiol. 5(1), 1-7.

Farr, S.A., Yamada, K.A., Butterfield, D.A., Abdul, H.M., Xu, L., Miller, N.E., Banks, W.A., Morley, J.E., 2008. Obesity and hypertriglyceridemia produce cognitive impairment. Endocrinology. 149(5), 2628-2636.

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., Koss, M.P., Marks, J.S., 1998. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am. J. Prev. Med. 14(4), 245-258.

Fergenbaum, J.H., Bruce, S., Lou, W., Hanley, A.J., Greenwood, C., Young, T.K., 2009. Obesity and lowered cognitive performance in a Canadian First Nations population. Obesity (Silver Spring). 17(10), 1957-1963.

Fernandes, B.S., Steiner, J., Bernstein, H.G., Dodd, S., Pasco, J.A., Dean, O.M., Nardin, P., Goncalves, C.A., Berk, M., 2016. C-reactive protein is increased in schizophrenia but is not altered by antipsychotics: meta-analysis and implications. Mol. Psychiatry. 21(4), 554-564.

Fink, A., Grabner, R.H., Benedek, M., Reishofer, G., Hauswirth, V., Fally, M., Neuper, C., Ebner, F., Neubauer, A.C., 2009. The creative brain: investigation of brain activity during creative problem solving by means of EEG and FMRI. Hum. Brain Mapp. 30(3), 734-748.

Fitzgerald, D., Lucas, S., Redoblado, M.A., Winter, V., Brennan, J., Anderson, J., Harris, A., 2004. Cognitive functioning in young people with first episode psychosis: relationship to diagnosis and clinical characteristics. Aust. N. Z. J. Psychiatry. 38(7), 501-510.

Foley, D.L., Morley, K.I., 2011. Systematic review of early cardiometabolic outcomes of the first treated episode of psychosis. Arch. Gen. Psychiat. 68(6), 609-616.

Friedman, J., 2016. The long road to leptin. J. Clin. Invest. 126(12), 4727-4734.

Friedman, J.I., Wallenstein, S., Moshier, E., Parrella, M., White, L., Bowler, S., Gottlieb, S., Harvey, P.D., McGinn, T.G., Flanagan, L., Davis, K.L., 2010. The effects of hypertension and body mass index on cognition in schizophrenia. Am. J. Psychiatry. 167(10), 1232-1239.

Fucetola, R., Newcomer, J.W., Craft, S., Melson, A.K., 1999. Age- and dose-dependent glucose-induced increases in memory and attention in schizophrenia. Psychiat. Res. 88(1), 1-13.

Gardiner, J.M., 1983. On recency and echoic memory. Philo. Trans. R. Soc. Lond. B Biol. Sci. 302(1110), 267-282.

Gatto, N.M., Henderson, V.W., St John, J.A., McCleary, C., Hodis, H.N., Mack, W.J., 2008. Metabolic syndrome and cognitive function in healthy middle-aged and older adults without diabetes. Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn. 15(5), 627-641.

Gluck, M.E., Ziker, C., Schwegler, M., Thearle, M., Votruba, S.B., Krakoff, J., 2013. Impaired glucose regulation is associated with poorer performance on the Stroop Task. Physiol. Behav. 122, 113-119.

Goldberg, T.E., Goldman, R.S., Burdick, K.E., Malhotra, A.K., Lencz, T., Patel, R.C., Woerner, M.G., Schooler, N.R., Kane, J.M., Robinson, D.G., 2007. Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: is it a practice effect? Arch. Gen. Psychiat. 64(10), 1115-1122.

Gonzalez-Blanch, C., Crespo-Facorro, B., Alvarez-Jimenez, M., Rodriguez-Sanchez, J.M., Pelayo-Teran, J.M., Perez-Iglesias, R., Vazquez-Barquero, J.L., 2007. Cognitive dimensions in first-episode schizophrenia spectrum disorders. J. Psychiatr. Res. 41(11), 968-977.

Gonzalez-Blanch, C., Crespo-Facorro, B., Alvarez-Jimenez, M., Rodriguez-Sanchez, J.M., Perez-Iglesias, R., Pelayo-Teran, J.M., Martinez-Garcia, O., Vazquez-Barquero, J.L., 2008. Lack of association between clinical and cognitive change in first-episode psychosis: the first 6 weeks of treatment. Can. J. Psychiatry. 53(12), 839-847.

Green, M.F., Harris, J.G., Nuechterlein, K.H., 2014. The MATRICS consensus cognitive battery: what we know 6 years later. Am. J. Psychiatry. 171(11), 1151-1154.

Green, M.F., Marder, S.R., Glynn, S.M., McGurk, S.R., Wirshing, W.C., Wirshing, D.A., Liberman, R.P., Mintz, J., 2002. The neurocognitive effects of low-dose haloperidol: a two-year comparison with risperidone. Biol. Psychiat. 51(12), 972-978.

Green, M.F., Nuechterlein, K.H., 2004. The MATRICS initiative: developing a consensus cognitive battery for clinical trials. Schizophr. Res. 72(1), 1-3.

Greenwood, C.E., Winocur, G., 2005. High-fat diets, insulin resistance and declining cognitive function. Neurobiol. Aging. 26 Suppl 1, 42-45.

Grundy, S.M., Cleeman, J.I., Daniels, S.R., Donato, K.A., Eckel, R.H., Franklin, B.A., Gordon, D.J., Krauss, R.M., Savage, P.J., Smith, S.C., Jr., Spertus, J.A., Costa, F., American Heart, A., National Heart, L., Blood, I., 2005. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 112(17), 2735-2752.

Gruzelier, J.H., 1999. Functional neuropsychophysiological asymmetry in schizophrenia: a review and reorientation. Schizophr. Bull. 25(1), 91-120.

Gunstad, J., Paul, R.H., Cohen, R.A., Tate, D.F., Gordon, E., 2006. Obesity is associated with memory deficits in young and middle-aged adults. Eat Weight Disord. 11(1), e15-19.

Gunstad, J., Paul, R.H., Cohen, R.A., Tate, D.F., Spitznagel, M.B., Gordon, E., 2007. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Compr. Psychiat. 48(1), 57-61.

Gunstad, J., Spitznagel, M.B., Paul, R.H., Cohen, R.A., Kohn, M., Luyster, F.S., Clark, R., Williams, L.M., Gordon, E., 2008. Body mass index and neuropsychological function in healthy children and adolescents. Appetite. 50(2-3), 246-251.

Guo, X., Zhang, Z., Wei, Q., Lv, H., Wu, R., Zhao, J., 2013. The relationship between obesity and neurocognitive function in Chinese patients with schizophrenia. BMC Psychiatry. 13, 109.

Gur, R.E., Gur, R.C., Skolnick, B.E., Caroff, S., Obrist, W.D., Resnick, S., Reivich, M., 1985. Brain function in psychiatric disorders. III. Regional cerebral blood flow in unmedicated schizophrenics. Arch. Gen. Psychiat. 42(4), 329-334.

Gur, R.E., Skolnick, B.E., Gur, R.C., Caroff, S., Rieger, W., Obrist, W.D., Younkin, D., Reivich, M., 1983. Brain function in psychiatric disorders. I. Regional cerebral blood flow in medicated schizophrenics. Arch. Gen. Psychiat. 40(11), 1250-1254.

Gustafson, T.B., Sarwer, D.B., 2004. Childhood sexual abuse and obesity. Obes. Rev. 5(3), 129-135.

Hair, N.L., Hanson, J.L., Wolfe, B.L., Pollak, S.D., 2015. Association of Child Poverty, Brain Development, and Academic Achievement. JAMA Pediatr. 169(9), 822-829.

Harrison, S.L., Ding, J., Tang, E.Y., Siervo, M., Robinson, L., Jagger, C., Stephan, B.C., 2014. Cardiovascular disease risk models and longitudinal changes in cognition: a systematic review. PLOS ONE. 9(12), e114431.

Harvey, J., 2007. Leptin regulation of neuronal excitability and cognitive function. Curr. Opin. Pharmacol. 7(6), 643-647.

Harvey, J., Shanley, L.J., O'Malley, D., Irving, A.J., 2005. Leptin: a potential cognitive enhancer? Biochem. Soc. T. 33(Pt 5), 1029-1032.

Harvey, P.D., Rabinowitz, J., Eerdekens, M., Davidson, M., 2005. Treatment of cognitive impairment in early psychosis: a comparison of risperidone and haloperidol in a large long-term trial. Am. J. Psychiatry. 162(10), 1888-1895.

Hasnain, M., Fredrickson, S.K., Vieweg, W.V., Pandurangi, A.K., 2010. Metabolic syndrome associated with schizophrenia and atypical antipsychotics. Curr. Diab. Rep. 10(3), 209-216.

Hassenstab, J.J., Sweat, V., Bruehl, H., Convit, A., 2010. Metabolic syndrome is associated with learning and recall impairment in middle age. Dement. Geritr. Cogn. 29(4), 356-362.

Heckers, S., Goff, D., Weiss, A.P., 2002. Reversed hemispheric asymmetry during simple visual perception in schizophrenia. Psychiat. Res. 116(1-2), 25-32.

Heinrichs, R.W., Zakzanis, K.K., 1998. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology. 12(3), 426-445.

Hepgul, N., Pariante, C.M., Dipasquale, S., DiForti, M., Taylor, H., Marques, T.R., Morgan, C., Dazzan, P., Murray, R.M., Mondelli, V., 2012. Childhood trauma is associated with increased Body Mass Index and increased C-reactive protein levels in first-episode psychosis patients. Psychol. Med. 42(9), 1893-1901.

Higgins, V., Adeli, K., 2017. Pediatric Metabolic Syndrome: Pathophysiology and Laboratory Assessment. EJIFCC. 28(1), 25-42.

Hill, S.K., Bishop, J.R., Palumbo, D., Sweeney, J.A., 2010. Effect of second-generation antipsychotics on cognition: current issues and future challenges. Expert Rev. Neurother. 10(1), 43-57.

Hill, S.K., Keshavan, M.S., Thase, M.E., Sweeney, J.A., 2004. Neuropsychological dysfunction in antipsychotic-naive first-episode unipolar psychotic depression. Am. J. Psychiatry. 161(6), 996-1003.

Holmen, A., Juuhl-Langseth, M., Thormodsen, R., Sundet, K., Melle, I., Rund, B.R., 2012. Executive function tests in early-onset psychosis: which one to choose? Scand. J. Psychol. 53(3), 200-205.

Hong, Z., Ng, K.K., Sim, S.K., Ngeow, M.Y., Zheng, H., Lo, J.C., Chee, M.W., Zhou, J., 2015. Differential age-dependent associations of gray matter volume and white matter integrity with processing speed in healthy older adults. NeuroImage. 123, 42-50.

Hopfinger, J.B., Buonocore, M.H., Mangun, G.R., 2000. The neural mechanisms of top-down attentional control. Nat. Neurosci. 3(3), 284-291.

Hottman, D.A., Chernick, D., Cheng, S., Wang, Z., Li, L., 2014. HDL and cognition in neurodegenerative disorders. Neurobiol. Dis. 72 Pt A, 22-36.

Huggins, A.W.F., 1975. Temporally segmented speech. Percept. Psychophys. 18(2), 149-157.

James, W., 1950. The principles of psychology. Dover Publications, [New York].

Johnsen, E., Fathian, F., Kroken, R.A., Steen, V.M., Jørgensen, H.A., Gjestad, R., Løberg, E.-M., 2016. The serum level of C-reactive protein (CRP) is associated with cognitive performance in acute phase psychosis. BMC Psychiatry. 16(1), 60.

Kahn, P.V., Walker, T.M., Williams, T.S., Cornblatt, B.A., Mohs, R.C., Keefe, R.S., 2012. Standardizing the use of the Continuous Performance Test in schizophrenia research: a validation study. Schizophr. Res. 142(1-3), 153-158.

Kaplan, G.A., Turrell, G., Lynch, J.W., Everson, S.A., Helkala, E.L., Salonen, J.T., 2001. Childhood socioeconomic position and cognitive function in adulthood. Int. J. Epidemiol. 30(2), 256-263.

Kasai, K., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Lee, C.U., Ciszewski, A.A., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2003. Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. Am. J. Psychiatry. 160(1), 156-164.

Keefe, R.S., 1995. The contribution of neuropsychology to psychiatry. Am. J. Psychiatry. 152(1), 6-15.

Keefe, R.S., Bilder, R.M., Harvey, P.D., Davis, S.M., Palmer, B.W., Gold, J.M., Meltzer, H.Y., Green, M.F., Miller, D.D., Canive, J.M., Adler, L.W., Manschreck, T.C., Swartz, M., Rosenheck, R., Perkins, D.O., Walker, T.M., Stroup, T.S., McEvoy, J.P., Lieberman, J.A., 2006. Baseline neurocognitive deficits in the CATIE schizophrenia trial. Neuropsychopharmacol. 31(9), 2033-2046.

Keefe, R.S., Fox, K.H., Harvey, P.D., Cucchiaro, J., Siu, C., Loebel, A., 2011. Characteristics of the MATRICS Consensus Cognitive Battery in a 29-site antipsychotic schizophrenia clinical trial. Schizophr. Res. 125(2-3), 161-168.

Keefe, R.S., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., Coughenour, L., 2004. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr. Res. 68(2-3), 283-297.

Keefe, R.S., Harvey, P.D., 2012. Cognitive impairment in schizophrenia. Handb. Exp. Pharmacol.(213), 11-37.

Kern, R.S., Gold, J.M., Dickinson, D., Green, M.F., Nuechterlein, K.H., Baade, L.E., Keefe, R.S., Mesholam-Gately, R.I., Seidman, L.J., Lee, C., Sugar, C.A., Marder, S.R., 2011. The MCCB impairment profile for schizophrenia outpatients: results from the MATRICS psychometric and standardization study. Schizophr. Res. 126(1-3), 124-131.

Kern, R.S., Nuechterlein, K.H., Green, M.F., Baade, L.E., Fenton, W.S., Gold, J.M., Keefe, R.S., Mesholam-Gately, R., Mintz, J., Seidman, L.J., Stover, E., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 2: co-norming and standardization. Am. J. Psychiatry. 165(2), 214-220.

Kiunke, W., Brandl, C., Georgiadou, E., Gruner-Labitzke, K., Horbach, T., Kohler, H., de Zwaan, M., Muller, A., 2013. Performance in neurocognitive tasks in obese patients. Does somatic comorbidity matter? Front. Psychiatry. 4, 84.

Koziol, L.F., Barker, L.A., Joyce, A.W., Hrin, S., 2014. Structure and function of large-scale brain systems. Appl. Neuropsychol. Child. 3(4), 236-244.

Kubovy, M., Howard, F.P., 1976. Persistence of a pitch-segregating echoic memory. J. Exp. Psychol. Hum. Percept. Perfrom. 2(4), 531-537.

Kuroki, N., Shenton, M.E., Salisbury, D.F., Hirayasu, Y., Onitsuka, T., Ersner-Hershfield, H., Yurgelun-Todd, D., Kikinis, R., Jolesz, F.A., McCarley, R.W., 2006. Middle and inferior temporal gyrus gray matter volume abnormalities in first-episode schizophrenia: an MRI study. Am. J. Psychiatry. 163(12), 2103-2110.

Lamport, D.J., Lawton, C.L., Mansfield, M.W., Dye, L., 2009. Impairments in glucose tolerance can have a negative impact on cognitive function: a systematic research review. Neurosci. Biobehav. R. 33(3), 394-413.

Lande, M.B., Kupferman, J.C., 2015. Cognitive function in hypertensive children. Curr. Hypertens. Rep. 17(1), 508.

Lavie, C.J., Milani, R.V., Ventura, H.O., 2009. Obesity and Cardiovascular Disease. J. Am. Coll. Cardiol. 53(21), 1925-1932.

Leeson, V.C., Harrison, I., Ron, M.A., Barnes, T.R., Joyce, E.M., 2012. The effect of cannabis use and cognitive reserve on age at onset and psychosis outcomes in first-episode schizophrenia. Schizophr. Bull. 38(4), 873-880.

Levin, B.E., Llabre, M.M., Dong, C., Elkind, M.S., Stern, Y., Rundek, T., Sacco, R.L., Wright, C.B., 2014. Modeling metabolic syndrome and its association with cognition: the Northern Manhattan study. J. Int. Neuropsych. Soc. 20(10), 951-960.

Li, C., Zhan, G., Rao, S., Zhang, H., 2014. Metabolic syndrome and its factors affect cognitive function in chronic schizophrenia complicated by metabolic syndrome. J. Nerv. Ment. Dis. 202(4), 313-318.

Liang, J., Matheson, B.E., Kaye, W.H., Boutelle, K.N., 2014. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int. J. Obes. (Lond). 38(4), 494-506.

Lindenmayer, J.P., Khan, A., Kaushik, S., Thanju, A., Praveen, R., Hoffman, L., Cherath, L., Valdez, G., Wance, D., 2012. Relationship between metabolic syndrome and cognition in patients with schizophrenia. Schizophr. Res. 142(1-3), 171-176.

Lorenz, W.F., 1922. Sugar Tolerance in Dementia Praecox and Other Mental Disorders. Arch. NeurPsych. 8(2), 184.

Lutgens, D., Lepage, M., Iyer, S., Malla, A., 2014. Predictors of cognition in first episode psychosis. Schizophr. Res. 152(1), 164-169.

Lv, Y.B., Yin, Z.X., Chei, C.L., Brasher, M.S., Zhang, J., Kraus, V.B., Qian, F., Shi, X.M., Matchar, D.B., Zeng, Y., 2016. Serum Cholesterol Levels within the High Normal Range Are Associated with Better Cognitive Performance among Chinese Elderly. J. Nurti. Health Aging. 20(3), 280-287.

Magistro, D., Takeuchi, H., Nejad, K.K., Taki, Y., Sekiguchi, A., Nouchi, R., Kotozaki, Y., Nakagawa, S., Miyauchi, C.M., Iizuka, K., Yokoyama, R., Shinada, T., Yamamoto, Y., Hanawa, S., Araki, T., Hashizume, H., Sassa, Y., Kawashima, R., 2015. The Relationship between Processing Speed and Regional White Matter Volume in Healthy Young People. PLOS ONE. 10(9), e0136386.

Malik, A.B., Shuaib, A., Turner, M.E., 2017. Neuropsychological Evaluation. http://emedicine.medscape.com/article/317596-overview.

Martinez-Cengotitabengoa, M., Mac-Dowell, K.S., Leza, J.C., Mico, J.A., Fernandez, M., Echevarria, E., Sanjuan, J., Elorza, J., Gonzalez-Pinto, A., 2012. Cognitive impairment is related to oxidative stress and chemokine levels in first psychotic episodes. Schizophr. Res. 137(1-3), 66-72.

McCleery, A., Addington, J., Addington, D., 2006. Substance misuse and cognitive functioning in early psychosis: a 2 year follow-up. Schizophr. Res. 88(1-3), 187-191.

McCleery, A., Ventura, J., Kern, R.S., Subotnik, K.L., Gretchen-Doorly, D., Green, M.F., Hellemann, G.S., Nuechterlein, K.H., 2014. Cognitive functioning in first-episode schizophrenia: MATRICS Consensus Cognitive Battery (MCCB) Profile of Impairment. Schizophr. Res. 157(1-3), 33-39.

McElroy, S.L., 2009. Obesity in patients with severe mental illness: overview and management. J. Clin. Psychiatry. 70 Suppl 3, 12-21.

McEvoy, J.P., Meyer, J.M., Goff, D.C., Nasrallah, H.A., Davis, S.M., Sullivan, L., Meltzer, H.Y., Hsiao, J., Scott Stroup, T., Lieberman, J.A., 2005. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr. Res. 80(1), 19-32.

McGurk, S.R., Mueser, K.T., 2004. Cognitive functioning, symptoms, and work in supported employment: a review and heuristic model. Schizophr. Res. 70(2-3), 147-173.

Meikle, A., Riby, L.M., Stollery, B., 2004. The impact of glucose ingestion and gluco-regulatory control on cognitive performance: a comparison of younger and middle aged adults. Hum. Psychopharmacol. 19(8), 523-535.

Messier, C., Awad-Shimoon, N., Gagnon, M., Desrochers, A., Tsiakas, M., 2011. Glucose regulation is associated with cognitive performance in young nondiabetic adults. Behav. Brain Res. 222(1), 81-88.

Minzenberg, M.J., Laird, A.R., Thelen, S., Carter, C.S., Glahn, D.C., 2009. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch. Gen. Psychiat. 66(8), 811-822.

Mitchell, A.J., Vancampfort, D., De Herdt, A., Yu, W., De Hert, M., 2013a. Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients. Schizophr. Bull. 39(2), 295-305.

Mitchell, A.J., Vancampfort, D., Sweers, K., van Winkel, R., Yu, W., De Hert, M., 2013b. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. Schizophr. Bull. 39(2), 306-318.

Moore, J.X., Chaudhary, N., Akinyemiju, T., 2017. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988-2012. Prev. Chronic Dis. 14, E24.

Morgan, V.A., Badcock, J., Waterreus, A., Galletly, C., Shah, S., Mackinnon, A., 2014. The role of cognition in metabolic disturbance in people with psychotic illness: Novel data from a large population prevalence survey. Schizophr. Res. 153, S223-S224.

Mortby, M.E., Janke, A.L., Anstey, K.J., Sachdev, P.S., Cherbuin, N., 2013. High "normal" blood glucose is associated with decreased brain volume and cognitive performance in the 60s: the PATH through life study. PLOS ONE. 8(9), e73697.

Murtagh, A., Hurley, A.L., Kinsella, A., Corvin, A., Donohoe, G., Gill, M., O'Callaghan, E., Murphy, K.C., 2010. The Letter-Number Sequencing Test and its association with potential to work among people with psychotic illness. Eur. Psychiatry. 25(2), 101-104.

Nagel, B.J., Herting, M.M., Maxwell, E.C., Bruno, R., Fair, D., 2013. Hemispheric lateralization of verbal and spatial working memory during adolescence. Brain Cogn. 82(1), 58-68.

Naguib, J.M., Kulinskaya, E., Lomax, C.L., Garralda, M.E., 2009. Neuro-cognitive performance in children with type 1 diabetes--a meta-analysis. J. Pediatr. Psychol. 34(3), 271-282.

Nasrallah, H.A., 2010. Linkage of cognitive impairments with metabolic disorders in schizophrenia. Am. J. Psychiatry. 167(10), 1155-1157.

Nelson, R.A., Bremer, A.A., 2010. Insulin resistance and metabolic syndrome in the pediatric population. Metab. Syndr. Relat. D. 8(1), 1-14.

Newcomer, J.W., 2005. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs. 19 Suppl 1, 1-93.

Newcomer, J.W., Craft, S., Fucetola, R., Moldin, S.O., Selke, G., Paras, L., Miller, R., 1999. Glucose-induced increase in memory performance in patients with schizophrenia. Schizophr. Bull. 25(2), 321-335.

Newcomer, J.W., Haupt, D.W., Fucetola, R., Melson, A.K., Schweiger, J.A., Cooper, B.P., Selke, G., 2002. Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. Arch. Gen. Psychiat. 59(4), 337-345.

Noble, K.G., Norman, M.F., Farah, M.J., 2005. Neurocognitive correlates of socioeconomic status in kindergarten children. Developmental Sci. 8(1), 74-87.

Nuechterlein, K.H., Barch, D.M., Gold, J.M., Goldberg, T.E., Green, M.F., Heaton, R.K., 2004. Identification of separable cognitive factors in schizophrenia. Schizophr. Res. 72(1), 29-39.

Nuechterlein, K.H., Dawson, M.E., 1984. Information processing and attentional functioning in the developmental course of schizophrenic disorders. Schizophr. Bull. 10(2), 160-203.

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., Essock, S., Fenton, W.S., Frese, F.J., 3rd, Gold, J.M., Goldberg, T., Heaton, R.K., Keefe, R.S., Kraemer, H., Mesholam-Gately, R., Seidman, L.J., Stover, E., Weinberger, D.R., Young, A.S., Zalcman, S., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am. J. Psychiatry. 165(2), 203-213.

O'Muircheartaigh, J., Dean, D.C., 3rd, Ginestet, C.E., Walker, L., Waskiewicz, N., Lehman, K., Dirks, H., Piryatinsky, I., Deoni, S.C., 2014. White matter development and early cognition in babies and toddlers. Hum. Brain Mapp. 35(9), 4475-4487.

Ohmann, S., Popow, C., Rami, B., Konig, M., Blaas, S., Fliri, C., Schober, E., 2010. Cognitive functions and glycemic control in children and adolescents with type 1 diabetes. Psychol. Med. 40(1), 95-103.

Okano, H., Hirano, T., Balaban, E., 2000. Learning and memory. Proc. Natl. Acad. Sci. U S A 97(23), 12403-12404.

Owen, A.M., Morris, R.G., Sahakian, B.J., Polkey, C.E., Robbins, T.W., 1996. Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Brain. 119 (Pt 5), 1597-1615.

Owen, L., Scholey, A., Finnegan, Y., Sunram-Lea, S.I., 2013. Response variability to glucose facilitation of cognitive enhancement. Brit. J. Nutr. 110(10), 1873-1884.

Owen, L., Scholey, A.B., Finnegan, Y., Hu, H., Sunram-Lea, S.I., 2012. The effect of glucose dose and fasting interval on cognitive function: a double-blind, placebo-controlled, six-way crossover study. Psychopharmacology (Berl). 220(3), 577-589.

Palmisano, G.L., Innamorati, M., Vanderlinden, J., 2016. Life adverse experiences in relation with obesity and binge eating disorder: A systematic review. J. Behav. Addict. 5(1), 11-31.

Panza, F., Frisardi, V., Capurso, C., Imbimbo, B.P., Vendemiale, G., Santamato, A., D'Onofrio, G., Seripa, D., Sancarlo, D., Pilotto, A., Solfrizzi, V., 2010. Metabolic syndrome and cognitive impairment: current epidemiology and possible underlying mechanisms. J. Alzheimers Dis. 21(3), 691-724.

Papanastasiou, E., 2013. The prevalence and mechanisms of metabolic syndrome in schizophrenia: a review. Ther. Adv. Psychopharmacol. 3(1), 33-51.

Pavlik, V.N., Hyman, D.J., Doody, R., 2005. Cardiovascular risk factors and cognitive function in adults 30-59 years of age (NHANES III). Neuroepidemiology. 24(1-2), 42-50.

Pencer, A., Addington, J., 2003. Substance use and cognition in early psychosis. J. Psychiatr. Neurosci. 28(1), 48-54.

Pettersson-Yeo, W., Benetti, S., Marquand, A.F., Dell'acqua, F., Williams, S.C., Allen, P., Prata, D., McGuire, P., Mechelli, A., 2013. Using genetic, cognitive and multi-modal neuroimaging data to identify ultra-high-risk and first-episode psychosis at the individual level. Psychol. Med. 43(12), 2547-2562.

Pettersson-Yeo, W., Benetti, S., Marquand, A.F., Joules, R., Catani, M., Williams, S.C., Allen, P., McGuire, P., Mechelli, A., 2014. An empirical comparison of different approaches for combining multimodal neuroimaging data with support vector machine. Front. Neurosci-Switz. 8, 189.

Pisella, L., Berberovic, N., Mattingley, J.B., 2004. Impaired working memory for location but not for colour or shape in visual neglect: a comparison of parietal and non-parietal lesions. Cortex. 40(2), 379-390.

Popkin, M.K., Colon, E.A., 2001. The interface of psychiatric disorders and diabetes mellitus. Curr. Psychiat. Rep. 3(3), 243-250.

Posner, M.I., Cohen, Y., Rafal, R.D., 1982. Neural systems control of spatial orienting. Philo. Trans. R. Soc. Lond. B Biol. Sci. 298(1089), 187-198.

Posner, M.I., Walker, J.A., Friedrich, F.A., Rafal, R.D., 1987. How do the parietal lobes direct covert attention? Neuropsychologia. 25(1a), 135-145.

Posner, M.I., Walker, J.A., Friedrich, F.J., Rafal, R.D., 1984. Effects of parietal injury on covert orienting of attention. J. Neurosci. 4(7), 1863-1874.

Potvin, S., Joyal, C.C., Pelletier, J., Stip, E., 2008. Contradictory cognitive capacities among substance-abusing patients with schizophrenia: a meta-analysis. Schizophr. Res. 100(1-3), 242-251.

Purdon, S.E., Jones, B.D., Stip, E., Labelle, A., Addington, D., David, S.R., Breier, A., Tollefson, G.D., 2000. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for Research in Schizophrenia. Arch. Gen. Psychiat. 57(3), 249-258.

Rabin, R.A., Zakzanis, K.K., George, T.P., 2011. The effects of cannabis use on neurocognition in schizophrenia: a meta-analysis. Schizophr. Res. 128(1-3), 111-116.

Rajji, T.K., Ismail, Z., Mulsant, B.H., 2009. Age at onset and cognition in schizophrenia: meta-analysis. The British journal of psychiatry : the journal of mental science 195(4), 286-293.

Ranganath, C., DeGutis, J., D'Esposito, M., 2004. Category-specific modulation of inferior temporal activity during working memory encoding and maintenance. Brain Res Cogn. Brain Res. 20(1), 37-45.

Rao, D.P., Dai, S., Lagace, C., Krewski, D., 2014. Metabolic syndrome and chronic disease. Chronic Dis. Inj. Can. 34(1), 36-45.

Raphael, T., Parsons, J., 1921. Blood Sugar Studies in Dementia Praecox and Manic-Depressive Insanity. Arch. NeurPsych. 5(6), 687-709.

Rapp, C., Studerus, E., Bugra, H., Aston, J., Tamagni, C., Walter, A., Pflueger, M., Borgwardt, S., Riecher-Rossler, A., 2013. Duration of untreated psychosis and cognitive functioning. Schizophr. Res. 145(1-3), 43-49.

Riediger, N.D., Clara, I., 2011. Prevalence of metabolic syndrome in the Canadian adult population. Can. Med. Assoc. J. 183(15), E1127-1134.

Robinson, H., Calamia, M., Glascher, J., Bruss, J., Tranel, D., 2014. Neuroanatomical correlates of executive functions: a neuropsychological approach using the EXAMINER battery. J. Int. Neuropsych. Soc. 20(1), 52-63.

Roper, L.J., Purdon, S.E., Aitchison, K.J., 2015. Childhood and later life stressors and psychosis. Clin. Neuropsychiatry J. Treat. Eval. 12(6), 148.

Roseberry, J.E., Kristian Hill, S., 2014. Limited practice effects and evaluation of expectation for change: MATRICS Consensus Cognitive Battery. Schizophr. Res. 159(1), 188-192.

Rund, B.R., Melle, I., Friis, S., Larsen, T.K., Midboe, L.J., Opjordsmoen, S., Simonsen, E., Vaglum, P., McGlashan, T., 2004. Neurocognitive dysfunction in first-episode psychosis: correlates with symptoms, premorbid adjustment, and duration of untreated psychosis. Am. J. Psychiatry. 161(3), 466-472.

Saddichha, S., Ameen, S., Akhtar, S., 2007. Incidence of new onset metabolic syndrome with atypical antipsychotics in first episode schizophrenia: a six-week prospective study in Indian female patients. Schizophr. Res. 95(1-3), 247.

Scarpina, F., Tagini, S., 2017. The Stroop Color and Word Test. Front. Psychol. 8, 557.

Scholes, K.E., Martin-Iverson, M.T., 2010. Cannabis use and neuropsychological performance in healthy individuals and patients with schizophrenia. Psychol. Med. 40(10), 1635-1646.

Schulingkamp, R.J., Pagano, T.C., Hung, D., Raffa, R.B., 2000. Insulin receptors and insulin action in the brain: review and clinical implications. Neurosci. Biobehav. R. 24(8), 855-872.

Segura, B., Jurado, M.A., Freixenet, N., Albuin, C., Muniesa, J., Junque, C., 2009. Mental slowness and executive dysfunctions in patients with metabolic syndrome. Neurosci. Lett. 462(1), 49-53.

Setayeshgar, S., Whiting, S.J., Vatanparast, H., 2012. Metabolic syndrome in canadian adults and adolescents: prevalence and associated dietary intake. ISRN Obes. 2012, 816846.

Shams, T.A., Muller, D.J., 2014. Antipsychotic induced weight gain: genetics, epigenetics, and biomarkers reviewed. Curr. Psychiat. Rep. 16(10), 473.

Shapiro, A.M., Benedict, R.H., Schretlen, D., Brandt, J., 1999. Construct and concurrent validity of the Hopkins Verbal Learning Test-revised. Clin. Neuropsychol. 13(3), 348-358.

Sims, R.C., Madhere, S., Gordon, S., Clark, E., Jr., Abayomi, K.A., Callender, C.O., Campbell, A.L., Jr., 2008. Relationships among blood pressure, triglycerides and verbal learning in African Americans. J. Natl. Med. Assoc. 100(10), 1193-1198.

Smith, M.A., Riby, L.M., Eekelen, J.A., Foster, J.K., 2011. Glucose enhancement of human memory: a comprehensive research review of the glucose memory facilitation effect. Neurosci. Biobehav. R. 35(3), 770-783.

Snyder, P.J., Jackson, C.E., Piskulic, D., Olver, J., Norman, T., Maruff, P., 2008. Spatial working memory and problem solving in schizophrenia: the effect of symptom stabilization with atypical antipsychotic medication. Psychiat. Res. 160(3), 316-326.

Sponheim, S.R., Jung, R.E., Seidman, L.J., Mesholam-Gately, R.I., Manoach, D.S., O'Leary, D.S., Ho, B.C., Andreasen, N.C., Lauriello, J., Schulz, S.C., 2010. Cognitive deficits in recent-onset and chronic schizophrenia. J. Psychiatr. Res 44(7), 421-428.

Spreen, O., 1998. A compendium of neuropsychological tests : administration, norms, and commentary, in: Strauss, E. (Ed.) 2nd ed. ed. Oxford University Press, New York :.

Squire, L.R., 2009. Memory and Brain Systems: 1969–2009. J. Neurosci. 29(41), 12711-12716.

Srihari, V.H., Phutane, V.H., Ozkan, B., Chwastiak, L., Ratliff, J.C., Woods, S.W., Tek, C., 2013. Cardiovascular mortality in schizophrenia: defining a critical period for prevention. Schizophr. Res. 146(1-3), 64-68.

Stuss, D.T., 2011. Functions of the frontal lobes: relation to executive functions. J. Int. Neuropsych. Soc. 17(5), 759-765.

Sumiyoshi, T., 2008. Possible dose-side effect relationship of antipsychotic drugs: relevance to cognitive function in schizophrenia. Expert Rev. Clin. Phar. 1(6), 791-802.

Tam, J.W., Schmitter-Edgecombe, M., 2013. The role of processing speed in the Brief Visuospatial Memory Test - revised. Clin. Neuropsychol. 27(6), 962-972.

Taylor, V.H., MacQueen, G.M., 2007. Cognitive dysfunction associated with metabolic syndrome. Obes. Rev. 8(5), 409-418.

Taylor, V.H., McIntyre, R.S., Remington, G., Levitan, R.D., Stonehocker, B., Sharma, A.M., 2012. Beyond pharmacotherapy: understanding the links between obesity and chronic mental illness. Can. J. Psychiatry. 57(1), 5-12.

Thiebaut de Schotten, M., Dell'Acqua, F., Forkel, S.J., Simmons, A., Vergani, F., Murphy, D.G., Catani, M., 2011. A lateralized brain network for visuospatial attention. Nat. Neurosci. 14(10), 1245-1246.

Thiebaut de Schotten, M., Dell'Acqua, F., Ratiu, P., Leslie, A., Howells, H., Cabanis, E., Iba-Zizen, M.T., Plaisant, O., Simmons, A., Dronkers, N.F., Corkin, S., Catani, M., 2015. From Phineas Gage and Monsieur Leborgne to H.M.: Revisiting Disconnection Syndromes. Cereb Cortex. 25(12), 4812-4827.

Toalson, P., Ahmed, S., Hardy, T., Kabinoff, G., 2004. The Metabolic Syndrome in Patients With Severe Mental Illnesses. Prim. Care. Companion J. Clin. Psychiatry. 6(4), 152-158.

Tombaugh, T.N., 2004. Trail Making Test A and B: normative data stratified by age and education. Arch. Clin. Neuropsychol. 19(2), 203-214.

Tournoy, J., Lee, D.M., Pendleton, N., O'Neill, T.W., O'Connor, D.B., Bartfai, G., Casanueva, F.F., Finn, J.D., Forti, G., Giwercman, A., Han, T.S., Huhtaniemi, I.T., Kula, K., Lean, M.E., Moseley, C.M., Punab, M., Silman, A.J., Vanderschueren, D., Wu, F.C., Boonen, S., group, E.s., 2010. Association of cognitive performance with the metabolic syndrome and with glycaemia in middle-aged and older European men: the European Male Ageing Study. Diabetes Metab. Res. Rev. 26(8), 668-676.

Troisi, A., 2009. Cholesterol in coronary heart disease and psychiatric disorders: same or opposite effects on morbidity risk? Neurosci. Biobehav. R. 33(2), 125-132.

Uttal, W.R., 2011. Mind and Brain: A Critical Appraisal of Cognitive Neuroscience. MIT Press.

van den Berg, E., Kloppenborg, R.P., Kessels, R.P., Kappelle, L.J., Biessels, G.J., 2009. Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity: A systematic comparison of their impact on cognition. Biochim. Biophys. Acta. 1792(5), 470-481.

Vancampfort, D., Correll, C.U., Galling, B., Probst, M., De Hert, M., Ward, P.B., Rosenbaum, S., Gaughran, F., Lally, J., Stubbs, B., 2016. Diabetes mellitus in people with schizophrenia, bipolar disorder and major depressive disorder: a systematic review and large scale meta-analysis. World Psychiatry. 15(2), 166-174.

Vancampfort, D., Wampers, M., Mitchell, A.J., Correll, C.U., De Herdt, A., Probst, M., De Hert, M., 2013. A meta-analysis of cardio-metabolic abnormalities in drug naive, first-episode and multi-episode patients with schizophrenia versus general population controls. World Psychiatry. 12(3), 240-250.

Vieira, J.R., Elkind, M.S., Moon, Y.P., Rundek, T., Boden-Albala, B., Paik, M.C., Sacco, R.L., Wright, C.B., 2011. The metabolic syndrome and cognitive performance: the Northern Manhattan Study. Neuroepidemiology. 37(3-4), 153-159.

Vincenzi, B., Stock, S., Borba, C.P., Cleary, S.M., Oppenheim, C.E., Petruzzi, L.J., Fan, X., Copeland, P.M., Freudenreich, O., Cather, C., Henderson, D.C., 2014. A randomized placebo-controlled pilot study of pravastatin as an adjunctive therapy in schizophrenia patients: effect on inflammation, psychopathology, cognition and lipid metabolism. Schizophr. Res. 159(2-3), 395-403.

Wardle, J., Rogers, P., Judd, P., Taylor, M.A., Rapoport, L., Green, M., Nicholson Perry, K., 2000. Randomized trial of the effects of cholesterol-lowering dietary treatment on psychological function. Am. J. Med. 108(7), 547-553.

Weickert, T.W., Goldberg, T.E., Marenco, S., Bigelow, L.B., Egan, M.F., Weinberger, D.R., 2003. Comparison of cognitive performances during a placebo period and an atypical antipsychotic treatment period in schizophrenia: critical examination of confounds. Neuropsychopharmacol. 28(8), 1491-1500.

Weickert, T.W., Goldberg, T.E., Mishara, A., Apud, J.A., Kolachana, B.S., Egan, M.F., Weinberger, D.R., 2004. Catechol-O-methyltransferase val108/158met genotype predicts working memory response to antipsychotic medications. Biol. Psychiat. 56(9), 677-682.

Wendt, P.E., Risberg, J., 1994. Cortical activation during visual spatial processing: relation between hemispheric asymmetry of blood flow and performance. Brain Cogn. 24(1), 87-103.

White, T., Stern, R.A., 2003. NAB: Psychometric and Technical Manual. Psychological Assessment Resources, Inc., Lutz, Florida, USA.

Wilde, N., Strauss, E., 2002. Functional equivalence of WAIS-III/WMS-III digit and spatial span under forward and backward recall conditions. Clin. Neuropsychol. 16(3), 322-330.

Wolf, P.A., Beiser, A., Elias, M.F., Au, R., Vasan, R.S., Seshadri, S., 2007. Relation of obesity to cognitive function: importance of central obesity and synergistic influence of concomitant hypertension. The Framingham Heart Study. Curr. Alzheimer Res. 4(2), 111-116.

Wysokiński, A., Dzienniak, M., Kłoszewska, I., 2013. Effect of metabolic abnormalities on cognitive performance and clinical symptoms in schizophrenia. Archives of Psychiatry and Psychotherapy. 4, 13-25.

Yates, K.F., Sweat, V., Yau, P.L., Turchiano, M.M., Convit, A., 2012. Impact of metabolic syndrome on cognition and brain: a selected review of the literature. Arterioscl. Throm. Vas. 32(9), 2060-2067.

Yau, P.L., Castro, M.G., Tagani, A., Tsui, W.H., Convit, A., 2012. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. Pediatrics. 130(4), e856-864.

Yucel, M., Bora, E., Lubman, D.I., Solowij, N., Brewer, W.J., Cotton, S.M., Conus, P., Takagi, M.J., Fornito, A., Wood, S.J., McGorry, P.D., Pantelis, C., 2012. The impact of cannabis use on cognitive functioning in patients with schizophrenia: a meta-analysis of existing findings and new data in a first-episode sample. Schizophr. Bull. 38(2), 316-330.

Yuste, R., 2015. From the neuron doctrine to neural networks. Nat. Rev. Neurosci. 16(8), 487-497.

Zaytseva, Y., Korsakova, N., Agius, M., Gurovich, I., 2013. Neurocognitive functioning in schizophrenia and during the early phases of psychosis: targeting cognitive remediation interventions. Biomed. Res. Int. 2013, 819587.

Zimmet, P., Alberti, K.G., Kaufman, F., Tajima, N., Silink, M., Arslanian, S., Wong, G., Bennett, P., Shaw, J., Caprio, S., Group, I.D.F.C., 2007. The metabolic syndrome in children and adolescents - an IDF consensus report. Pediatr. Diabetes. 8(5), 299-306.