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Phasic Electrodermal Activity in Schizophrenia: Skin Conductance Response in Unmedicated Schizophrenic Patients in Comparison to Normal Controls

by

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Abstract

Stimulus-elicited (phasic) skin conductance responses (SCRs) to indifferent stimuli have often been employed to examine abnormalities in orienting (allocation of attention) in studies of schizophrenia. Most previous studies have examined phasic activity only during habituation paradigms. Interpretation of many studies is complicated because patients are medicated during testing. In this study cross-modal orienting response dishabituation paradigm was presented to 68 normal controls and 47 unmedicated schizophrenia patients while SCRs were recorded. Gender and laterality (bilateral recording in right-handed participants) were varied between- and within-subjects, respectively. Overall reactivity, and the following four discrete attentional effects were examined: habituation; reinstatement; "super reinstatement"; and dishabituation. For all participants, overall reactivity was lower for schizophrenics than for normal controls, as indexed by both amplitude- and response frequency-based measures. For SCR responders only, overall responsivity did not differ between groups. For SCR responders, habituation, reinstatement, and dishabituation were evident across groups. Super reinstatement approached significance.

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Abbreviations:

CNS	Central Nervous System
EDA	Electrodermal Activity
FPV	Finger Pulse Volume
NSR	Nonspecific Response
OR	Orienting Response
SCL	Skin Conductance Level
SCOR	Skin Conductance Orienting Response
SCR	Skin Conductance Response

I. INTRODUCTION

I.1 FOREWARD

Interest in identifying electrical currents in the body and in particular electrical changes in the skin began over 100 years ago. Charcot along with Vigouroux (1879, 1888) measured tonic skin resistance levels in patients as a possible clinical diagnostic marker. The Russian physiologist Tarcanoff (1890) advanced this research by measuring electrical potential between two electrodes placed on the skin without applying an external electrical current. These discoveries formed the fundamental scientific basis of recording electrodermal activity (EDA) as it is done today (for review see Dawson et al., 2000).The use of skin conductance response (SCR) has expanded across medical research and in particular to psychiatric research. Indeed this peripheral, easy to use and non-invasive methodological tool contributed to initially advancing and to understanding the neurophysiology of psychiatric disorders. With the contributions of the research of Sokolov (1960, 1963) and other scientists, SCR became one of the most widely used dependent variables in the study of orienting and habituation. Several such studies have been done in the area of schizophrenia, but in most cases the patients were taking medication and phasic acitivity was studied only during habituation paradigms. The project described in this thesis explored the use of a more comprehensive electrodermal study in a comparison of unmedicated patients diagnosed with schizophrenia compared to healthy volunteers.

I.2 HISTORY OF EDA

Electrodermal activity (EDA), also known as galvanic skin response (GSR), provides a means to measure the electrical conductance of the skin, which varies with its moisture level. The sweat glands are controlled by the sympathetic nervous system (Martini, 2003) so skin conductance is used as an indication of psychological or physiological arousal. EDA has intrigued schizophrenia researchers due to its hypothesized relationship to processes considered dysfunctional in schizophrenia, including "arousal," "attention," "information processing," "emotion," and "habituation." For example, electrodermal differences between schizophrenic patients and normal controls were studied in the laboratory of Eugene Bleuler using Jung's word association test as early as the first decade of the last century (Paterson and Jung, 1907; Ricksher and Jung, 1907–08).

The skin is a giant organ and has as many physiological functions as of most other parts of the human body. The psychological correlation between the skin and perception of the outside world is remarkable. The skin is a protective barrier that helps protect the body's organ system, blood and fluid balance; it aids in vascular constriction and dilation through the process of perspiring. In fact, changes in skin tone, color and texture in response to stimuli are among one of the most fascinating pieces of empirical evidence that exists concerning the complexity of the nervous system and the brain.

EDA concerns electrical phenomena in the skin and has to do with active and passive electrical properties of the skin and is quantifiable and easily measured. Measurement of EDA is relatively non-invasive and can be done in less time than some other types of testing. It can be used to study many aspects including cognition, affect and individual differences. It can also be used in ambulatory studies. There are many dependent measures that may be observed with EDA and these different parts of EDA

appear to show different kinds of cognitive or affective response. When studying EDA, a measurement is taken of the function of the eccrine sweat glands, which believed to be involved in emotion-evoked sweating. The preferred way of monitoring EDA is often a measure of electrical conductance rather than resistance. EDA is associated with changes in the levels of hydration in the sweat glands. When the sweat glands fill with salt-water the skin will show less resistance and vice versa.

There are two types of measurement that are commonly used in studying EDA. The first is endosomatic measurement, which tends to be the more invasive of the two techniques and involves microneurography, i.e. the application of tiny electrodes that are placed directly on the sympathetic skin neurons. This method gives a direct measurement of the electrical activity of the skin's neurons. This measurement records both uniphasic and bi-phasic responses; the data collected bear a resemblance to data collected on an EEG. Exosomatic measurement basically involves placing two electrodes on the skin's surface and passing an electrical signal that is very small over the surface between the two electrodes and recording the skin potential response. The exosomatic method may be just as effective as the endosomatic method because there is such a strong correlation between skin neuron firing rates and actual skin conductance.

There are several important aspects of EDA reported in the literature and used in studying various psychiatric conditions. These include skin conductance level (SCL), skin conductance response (SCR), spontaneous or non-specific SCR (NS-SCR), latency and amplitude of the SCR. SCL is the absolute level of resistance or conductance at a given moment in the absence of a measurable phasic response (Dawson, 2000). The transient change that is measured over seconds is the stimulus-elicited skin conductance response (SCR). The most relevant aspect of the SCR for schizophrenia research is its frequency and rate of habituation (Dawson, 1992). Habituation involves a decline in SCR amplitude

and eventual disappearance with repetition of the eliciting stimulus (Dawson, 2000). See table 1.

Table 1: Common EDA measures

Measure	Definition	Typical Value
Skin Conductance Level (SCL)	Tonic level of electrical conductivity of the skin	2-20 uS
Skin Conductance Response (SCR)		
Frequency of NS SCR	Number of SCRs in the absence of identifiable eliciting stimulus	1-3 per mint
SCR amplitude	Phasic increase in conductance shortly following stimulus onset	0.2-1.0 uS
SCR latency	Temporal interval between stimulus onset and SCR initiation	1-3 sec
SCR half recovery time	Temporal interval between SCR peak and point of 50% recovery of SCR amplitude	2-10 sec
SCR habituation (trials to habituate)	Number of stimulus presentations before 2 or 3 trials with no response	2-8 stimulus presentation

The SCR has been a frequently employed index of the orienting response (OR). The orienting response (OR), also called the orienting reflex, is an organism's immediate response to a change in its environment, when that change is not sudden enough to elicit the startle reflex.

Ivan Pavlov, who referred to this response as the “What is it?" reflex, coined the term. In the 1950s the orienting response was studied systematically by the Russian scientist Eugene Sokolov, who documented the phenomenon called "habituation", referring to a gradual "familiarity effect" and reduction of the OR with repeated stimulus presentations (Sokolov 1960). According to Sokolovian theory, OR habituates to stimulus repetition and increases (is "reinstated") to stimulus change, provided that the stimuli in question are weak. The sensitivity of the response pattern to change in stimulation led Sokolov to identify it with occurrence of the OR, and to propose a mechanism for its elicitation in terms of a mismatch between stimulus input and the traces of previous stimulation stored in a "neuronal model ." In Sokolov's view, occurrence of an OR was "a sign that the nervous system has detected a change in the stimulus" (Sokolov, 1963, O'Gorman, 1979).

The initial research using skin conductance orienting response (SCOR) was important because it suggested a very important paradigm based on the basic identification of two distinct subgroups within the schizophrenic population. One group was a SCOR nonresponsive and this was associated with amygdaloid dysfunction and the other group was OR nonhabituating which was associated with hippocampal dysfunction (Bernstein 1982). The initial recordings of SCR led researchers to conclude that the limbic dysfunction likely existed in the left hemisphere
(Bernstein 1982).

The most consistent abnormal finding with schizophrenia patients has been SCR nonreponse to indifferent stimuli compared to normal controls. In reviewing about 30

studies, Ohman (1981) concluded that the average incidence of nonresponse in schizophrenics was close to 40%. Most previous studies have examined phasic activity to stimulus repetition only (i.e., "habituation paradigms"), and many studies have used unilateral recordings which do not allow assessment of possible laterality influences. There several studies that report lateral asymmetry of electrodermal responses in schizophrenic patients. Larger right than left-hand electrodermal responses were consistently found when patients passively listened to moderate intensity sounds (Gruzelier and Manchanda, 1982). Sex differences in OR have also been reported, including faster habituation and larger SCR in females (Guimaraes et al., 1991) and higher overall SCL in male schizophrenic patients compared to female patients (Zahn & Pickar, 2005).

In our study, we used a cross-modal (auditory-visual) OR dishabituation paradigm, which Furedy (1968) developed in order to study possible abnormalities in attentional processes in schizophrenia. The schizophrenic group was unmedicated to exclude the possible confounding effect of neuroleptic medications. We also examined lateralization and gender differences in OR between groups.

I.3. HISTORICAL SIGNIFICANCE OF ELECTRODERMAL RESPONSES

In the history of psychophysiology, measurement of electrodermal responses is a widely used and abused concept. The early discovery of electrodermal responses is more than one hundred years old and has been closely linked to psychological and cognitive functions of emotions, arousal and attention. Jean Charcot, a French neurologist, began noticing correlations in human skin changes over one hundred years ago in his experiments to measure objectively the emotional aspects of "hidden complexes". Fere (1888) and Tarchanoff (1890) discovered two basic tools of examination that are in use today; these responses are called the exosomatic response and the endosomatic response.

The tonic level of skin or SCL resistance or conductance is the absolute level of resistance or conductance at a given moment in the absence of a measurable phasic response. Superimposed on the tonic level are phasic decreases in resistance (increases in conductance) or SCR (Dawson, 2000).

The study of OR in schizophrenics started in the 1960's. The initial work was began in the Soviet Union by Sokolov who asserted that the OR is associated with the very onset of attention, triggered by the detection of any stimulus "novelty" (Sokolov, 1960, 1963). Luria (1973) called the OR "the most elementary form of attention".

The majority of research supports the existence of a strong link between the OR and attention. The OR is central to controlling what parts of the system are actually controlling a particular flow of events and what will gather attention to central processing and learning. Research suggests that the OR has a limited capacity as a central processor that is in operation only after the activation of pre-attentional automatic and processing channels. Presentation of a novel, unexpected, or significant stimulus typically elicits a constellation of motor, autonomic and central nervous system (CNS) responses collectively referred to as the "orienting response"(OR)(Dawson, 1984). According to Sokolov the OR is associated with identifiable responses in skin conductance, finger pulse volume, papillary dilation, cardiac deceleration, alpha-blockade and changes in skeletal muscle activity, including changes in respiration pattern. SCR is one of the most reliable indices of the OR, occurring at the first presentation of a novel stimulus in 95% of normal subjects (Lynn, 1966). The SCR-OR (or SCOR) reflects a phasic increase in sympathetic arousal thought to be related to a subject's attention to, and cognitive processing of, the eliciting stimulus and possibly related to improved processing of subsequently presented stimuli (Sokolov, 1963; Ohman, 1979).

The application of skin electrodes is not only useful for obtaining vital aspects of attention, but also for studying differences between different types of schizophrenic patients, making it possible to identify progression, stages and types of schizophrenia. Zahn (1968) found greater loss of SCOR in hebephrenic than in paranoid schizophrenic patients, a finding confirmed by Bernstein (1969). Bernstein (1964, 1969) reported that the vast majority of patients who display cognitive disorganization show more frequent SCOR and are “nonresponders” to certain types of insignificant stimuli than those patients who are more cognitively intact.

In the 1960s, there was a major conflict in SCOR findings in schizophrenic patients, typified on one side by the work of Bernstein (1969) reporting deficient OR in schizophrenia, with many patients unresponsive and others showing abnormally rapid habituation and by Zahn’s work (1964) on the other side, indicating that while heightened initial nonresponding occurred, schizophrenic patients were essentially over-reactive, showing a failure to habituate OR or an unstable habituation (Bernstein,1989). Gruzelier and Venables (1972) suggested a resolution to this conflict, and attributed these conflicting findings to a "bimodality hypothesis". They argued that schizophrenia exists in roughly equal numbers of a subgroup that fails to respond to innocuous stimuli and another essentially unable to stop responding (Venables 1975; Bernstein 1986).

I.3.1 THE CURRENT PERSPECTIVE

The latest research on this aspect of schizophrenia has been centered on the role of gender differences. Male schizophrenic subjects seem to suffer from earlier onset than female (Rosenthal 1970; Jablensky et al., 1992; Hafner et al., 1998a; Hafner et al., 1998b). Males also have more negative symptoms and tend to demonstrate a much more severe acute form of the schizophrenic illness (Angermeyer et al., 1990; Goldstein et al., 1990; Ragland et al., 1999).

There are conflicting results regarding EDA findings in schizophrenic patients versus normal subjects. However, most reviews have concluded, with some exceptions, a higher SCL and slow habitation of SCOR in schizophrenic patients (Zahn 1981a). In another study, Zahn (2005) reported that unmedicated male schizophrenic patients showed slight or no improvement during hospital stays; the patients who showed signs of improvement, both male and female, had a higher initial skin temperature.

Perhaps one of the most interesting findings in schizophrenia SCOR research is the phenomenon of nonresponders to innocuous stimuli. This finding has been universally replicated. It is interesting to note that in six international laboratories in the West roughly 40%-50% of the population in the sample was reported to respond poorly to innocuous stimuli of moderate intensity (Bernstein, 1987). These findings were consistent no matter if subjects had frequent hospitalizations or if they were being placed in the hospital for the first time. The fact that a patient was medicated or not medicated was also of little consequence. There appears to be a powerful link that exists between the OR and attentional responses. The majority of research seems to sustain this fact, leading Ohman (1979) to conclude that the OR "is central to the systems controlling what aspects of the flow of events will receive attention, central processing, and learning". Research seems to suggest that the OR has a limited capacity central processor that is in operation only after the activation of pre-attentional automatic and processing channels not in the central OR.

Most previous studies have focused on the SCOR to novel but innocuous tones. Studies report that 50% or more of patients with schizophrenia fail to give SCORs to the first two or three tones and are classified as nonresponders (Bernstein et al., 1982; Zahn, 2005). The clinical implications of this finding are still not quite clear. In one group of studies nonresponders showed higher ratings on both positive and negative symptoms than responders (Dawson & Neuchterlein, 1984). In mixed groups of medicated and

unmedicated patients and chronic and acute patients, nonresponders were reported to have higher scores than responders on Emotional Withdrawal and Conceptual Disorganization but lower on Excitement (Straube 1979; Bernstein 1981; Kim 1993; Zahn 1997).

In several studies, however, SCORs were not related significantly to symptoms. These include studies on unmedicated patients (Zahn 1981), medicated patients (Schiffer 1996) and those in which only some patients were medicated (Alm, 1984). Only a few studies controlled for the anti-cholinergic effect of the drugs (Green 1989; Perry 1995; Schlenker 1995). Finally, in contrast to the first group of studies, a few studies have reported more psychopathology in more responsive patients. Gruzelier (1976) reported that in patients with less than five years hospitalization, ward nurses rated Rs as more manic, anxious, assaultive, and attention demanding than NRs; there were no such differences in a very chronic group (Zahn 2005). In thirteen unmedicated chronic inpatients, only two of whom were NRs, ratings of overall severity were higher in non-habituators than in habituators (Deakin 1979). Bartfai (1987) reported that in 18 medicated patients, non-habituators had more auditory hallucinations than habituator Rs and NRs, but there were no differences on more global Psychopathology Rating Scale (CPRS) factors (Zahn, 2005).

Overall, these studies are inconclusive about if and how the SCOR relates to psychopathology. Differences among studies in medication, chronicity, or methodology by themselves do not seem able to account for the marked variability in findings (Zahn, 2005). For example, tone intensity ranged from 60 dB to 85 dB in all three groups of studies. It may be of interest that more symptoms were reported in less responsive patients in three of the four samples of unmedicated patients, but these had small sample sizes and in two of these (Bartfai 1984; Zahn 1997) the samples may be atypical (no NRs and childhood onset patients, respectively). (Zahn 2005). The differences between the

two studies from Bartfai's laboratory (Bartfai 1984, 1987), in which the patients differed in both medication and chronicity, suggest possible interactions between these two variables. About the most definite conclusion is that there is no support for differential relationships of the SCOR to positive and negative symptoms (Zahn, 2005).

Barry (2004) conducted some of the most recent research in this field. His initial experiments took place in 1993 and reported an initial increase in the OR after the very first stimulus presentation; this was followed by habituation. These results were successfully replicated by Barry in 2004, leading to the conclusion that the effect was not related to the first stimulus but a tonic effect of the first stimulus. In 1983 Lacono and Lykken foundd that a very loud stimulus (110 db) made the patient threshold-sensitive. This was not the innocuous stimulus that was used in OR research.

There is an important effect that can be inferred from Sokolov's theory in 1963 and this is the incidence of dis-habituation, which is an increased response to a repeated stimulus, which immediately follows the stimulus change. This also occurred once the trial was changed. The vast majority of discoveries of studies in EDA have involved large clinical groups and normal controls who have been presented with a repeating series of neutral stimuli, which are generally tones or high intensity lights. In fact, on the subject of habituation the studies focus on the dependent measures of the phasic and response habituation rate coupled with the response to stimuli. SCL has long been utilized as an index of central nervous system (CNS) arousal (e.g., Lykken & Venables, 1971; Raine et al 2002; Raskin, 1973). EEG (Barry et al., 2004; Barry et al 2007) and functional imaging studies (e.g., Critchley 2002; Fredrikson et al., 1998; Nagai et al 2004) have highlighted the close connection between central and peripheral SCL-based indices of arousal. Insights into the neuronal basis of SCR have come from brain lesion studies, electrical stimulation, and functional imaging. Impaired SCR is reported in patients with discrete brain lesions of the right hemisphere (Oscar-Berman and Gade, 1979; Zoccolotti

et al., 1982) and of the bilateral ventromedial prefrontal cortex, bilateral anterior cingulate gyrus, right inferior parietal lobe (Tranel and Damasio, 1994), and amygdala (Bechara et al., 1995). Lesions to the amygdala, a region anatomically and functionally interconnected with the ventromedial prefrontal cortex, also impair SCR during aversive conditioning and reward-related feedback (Bechara et al., 1999), but not in response to unconditioned aversive stimuli (Tranel and Damasio, 1989). Ventromedial prefrontal lesions, like amygdala lesions, impair anticipatory SCR during risk-related decision making, but unlike amygdala lesions they do not impair SCR elicited by reward-related feedback (Bechara et al., 1999). Modulation of SCR can also be elicited by electrical stimulation of the amygdala, hippocampus, anterior cingulate, and frontal cortex (Mangina and Beuzeron-Mangina, 1996). Positive correlations between SCR and neural activity in motor cortex and mid-cingulate in subjects experiencing emotive stimuli are reported in functional imaging studies (Fredrikson et al., 1998). In an event-related functional magnetic resonance imaging (fMRI) study, activity in the amygdala and insula reflected acquisition of aversive conditioning, indexed by SCR (Buchel et al., 1998)

Functional MRI (Hugo et al., 2000) has been used to study brain activity associated with spontaneous fluctuations in amplitude of SCR and activity corresponding to generation and afferent representation of discrete SCR events. Regions that covaried with increased SCR included the right orbitofrontal cortex, right anterior insula, left lingual gyrus, right fusiform gyrus, and left cerebellum. Generation of discrete SCR events was associated with significant activity in the left medial prefrontal cortex, bilateral extrastriate visual cortices, and cerebellum. Activity in the right medial prefrontal cortex was related to afferent representation of SCR events. Activity in the bilateral medial prefrontal lobe, right orbitofrontal cortex, and bilateral extrastriate visual cortices was common to both generation and afferent representation of discrete SCR events identified in a conjunction analysis. These results suggest that areas implicated in emotion and

attention are differentially involved in generation and representation of peripheral SCR responses which may reflect ongoing integrated emotional and attentional states of the organism (Hugo et al., 2000)

I.3.2 NONRESPONDERS

Berstein (1982) found that NRs had high levels of emotional withdrawal and a general sense of cognitive disorganization. There was definitely a correlation between NRs and negative symptoms. The correlation between the lowered OR and social and emotional abstinence does not seem to be a direct relation to being hospitalized, being on medication or being diagnosed schizophrenic. There are other interesting findings that appear to define schizophrenic NRs. Schineider (1982) concludes that among acute and chronic schizophrenic patients who show more negative symptoms and show poor OR, NRs tend to have more blood relatives who also suffer from schizophrenia. The vast majority of Rs are usually the only case within their family.

In 1977 Zubin and Spring proposed the stress-vulnerability model for schizophrenia. It proposes that each individual has unique biological, psychological and social elements. These elements include strengths and vulnerabilities for dealing with stress. Researchers investigated SCOR in NRs as a biological vulnerability marker and its temporal stability. Iacono (1982) and Zahn (1981) reported the incidence of SCOR non-response to remain the same after clinical remission. Based on this evidence, Dawson and Nuechterlein (1984) concluded that OR non-responding was a promising vulnerability marker of a genetic disposition. Bernstein (1987) came to the conclusion that in seven major studies almost half of the schizophrenic subjects were SCOR nonresponders when presented with non-signal, innocuous and mild auditory stimuli.

There are certain traits that seem to be consistent among all schizophrenic nonresponders. A large number of studies have found that responders tend to have a higher SCL, a larger

number of non-specific responses (NSRs) than the vast majority of nonresponders and higher measurements in response systems (e.g. heart rate and event-related brain potentials). These findings lead researchers to believe that there may possibly be a subtype of schizophrenia that is exclusively unique to nonresponders. The basic criteria for this assumption were that the nonresponse should exist both before and after an episode. Zahn (1982) used this as a means to mark patients at general risk.

In 1986 Bernstein found that schizophrenic patients generally were nonresponsive to innocuous tones in both the SCR as well as in Finger Pulse Volume (FPV) measures. However, SCOR non-responders were found to respond to higher intensity stimuli. These findings were consistent with earlier findings which reported that the vast majority of schizophrenic patients were nonresponsive to innocuous stimuli in SCR, FPV and the dilation of the pupils (Bernstein 1986). These response systems are all tied together and each holds an important component of the OR. There are, of course, other relevant factors such as medication regime that must be taken into account when looking at overall responsiveness.

The anticholinergic effect of neuroleptic medications on SCOR has received a lot of attention. Zahn et al. (2001) show that not only increased but also decreased anti-cholinergic effects of medication can influence EDA findings between patients. (Zahn, 1986; Zahn et al., 1991; Zahn et al., 2001; Zahn & Pickar, 2005). Neuroleptic medications reduce EDA and no study examining neuroleptic effects on schizophrenic patients has reported treatment-associated increases in EDA (Schnur 1990). SCL reduction is the most robust effect of neuroleptic medications, and to a lesser extent there is a reduction in SF frequency. Both are indices of tonic EDA and may vary with the effect of neuroleptics with high anticholinergic effects. However, neuroleptic effects on phasic EDA have been less uniformly demonstrated. Schunr (1990), in his review, reported two out of seven studies which showed slight positive change in the SCOR

responder status from NR to R. The bulk of evidence suggests that SCOR responders' status does not vary robustly with neuroleptic treatment. However, it may be possible that the prevalence of SCOR non-responding is increased with administration of neuroleptics with strong anti-cholinergic effects (Schuner,1990). Zahn et al (2001) studied the effect of neuroleptics using between-group analyses—patients taking placebo were compared with patients taking fluphenazine and with control subjects using only data from the first test session; they also used within-subjects analyses in which the same patients were tested when taking fluphenazine and when taking placebo. They found elevated indexes of resting autonomic activation, small tonic and phasic responses to significant situations and stimuli, and slow habituation rates of SCORs. They failed to replicate findings of attenuated orienting and a high incidence of electrodermal "nonresponding", which has been frequent findings in numerous previous studies on similar sample of patients reviewed by Schuner, 1990.

Some research in this area has been primarily interested in gender differences (Leung & Chue, 2001; Tamminga, 1997; summary by Slewa-Younan et al., 2004). The vast majority of evidence indicates that male patients have earlier onset and more negative symptoms than female patients (Rosenthal, 1970; Jablensky et al., 1992; Hafner, et al., 1998a; Hafner et al., 1998b). It has been further proven that male patients have a more acute psychotic pathology, while females tend to be more depressed than their male counterparts (Desai & Jann, 2001; Kessler, 2003; Kornseit et al., 2000).

Few studies have investigated possible gender differences in SCL or SCR with schizophrenics. Zahn et al., (1981a) reported slow phasic (SCR) and tonic (prestimulus SCL) habituation to mild (72 dB) non-signal tones with female drug-free patients. In a related study, Zahn et al. (1981b) found that unmedicated male schizophrenics who showed moderate or no improvement during subsequent hospital treatment on the basis of nurses' and psychiatrists' ratings of severity of psychopathology displayed slower SCL

decline over habituation trials relative to normal controls and male patients who showed improvement on the same ratings. In the latter study, 'unimproved' male patients also had higher resting baseline SCL than the other male groups. 'Improved' schizophrenics (males and females) had a higher initial skin temperature level (STL) than normals, but data regarding changes over trials for STL was not reported. No differential effects for STL during neutral stimulation were reported in either study. Zahn & Pickar (2005) found that unmedicated male schizophrenic patients had higher average SCL than female patients during resting and neutral tone conditions, whereas women had greater SCR magnitude than men to signal (reaction time) stimuli. With the exception of the above studies by Zahn et al. (1981a; 1981b) and a study by Iacono et al. (1984) which reported no differential effects of gender for SCR habituation rate and overall average SCL with remitted depressive patients, no other studies have been located which examined the possible effects of gender during habituation of SCR or SCL components of orienting with depressive patients or schizophrenic patients.

I. 3.3. TYPES OF EDA PARADIGM

Dawson (2007) identified three general types of paradigms in which EDA is frequently used: 1) the presentation of discrete stimuli, 2) the presentation of chronic stimuli, and 3) the measurement of individual differences in EDA.

a. Paradigm One: Orienting Response Habituation

The 'orienting response habituation' paradigm, most commonly used in psychophysiology research, entails "measuring the elicitation and habituation of various indices of the orienting response, of which the SCR is a reliable and easily measurable component" (Dawson et al., 2000). In its specific application, the 'orienting response habituation' paradigm "consists of the repetitive presentation of a simple discrete

innocuous stimulus (commonly a 1-sec tone of approximately 75dB) with interstimulus intervals varying between 20 sec and 60 sec)" (Dawson et al., 2000). Generally, the most pertinent findings in these studies are that SCR declines in volume and the shape of the response changes with stimulus repetition, thus creating a response system which is inevitably less active and less reactive.

In the 'orienting response habituation' paradigm, study results observed are consistent with the notion that "the SCR is highly sensitive to stimulus significance", although there remain slight discrepancies (Dawson et al., 2000). EDA is widely measured using a discrete stimulus paradigm termed 'discrimination classical conditioning', which highlights the influence of stimulus significance while controlling for stimulus novelty (Dawson et al., 2000). In 1970, Seligman investigated preparedness and conditioning in normal subjects. The core idea of preparedness is that "some associations (such as the association between taste and nausea, or perhaps faces and affect) are, because of their survival value for the organism, much more easily and strongly established than others, such as that between an arbitrary tone and a shock. Extending Seligman's work, Ohman (1975) and his colleagues applied this concept to human autonomic conditioning, using 'biologically prepared', 'potentially phobic', or 'fear-relevant' conditioned stimuli. Ohman (1981) found that "cognitive manipulations or processes that would be expected to dramatically reduce the conditioned SCR have a lesser impact on responses conditioned to these potentially phobic stimuli. Fearful images of snakes and spiders had a greater impact on the conditioned SCR than had fear-irrelevant images of triangles and circles (Dawson et al., 2000).

While several studies such as that of Dawson and Schell (1973) propose the hypothesis that "conscious awareness is necessary for the initial learning of stimulus significance but not for the later evocation of SCRs to previously learned significant stimuli" (Dawson et al., 2000), other researchers have shown this is not necessarily true.

While the Dawson-Schell conjecture is provocative, Tranel & Damasio (1985, 1993), in their studies on prosopagnosia and recognition of faces, have shown that for some subjects under certain conditions, affective associative learning as a conditioned stimulus may occur without apparent conscious awareness (Dawson et al., 2000). Despite conflicting findings, researchers studying SCRs elicited from habituation stimuli will continue to explore their implications for theories of emotional learning.

b. Paradigm Two: Chronic Stimuli

The next paradigm, which involves the delivery of a continuous stimulus or a situation requiring the performance of a sustained task, has demonstrated the sensitivity of EDA to simple manipulation tactics. Studies have shown that the ongoing task (e.g. requiring a group of subjects to perform a series of arithmetic problems) and power of threat (e.g. where a second group of subjects is threatened with delivery of electric shock for poor performance on the arithmetic task) produce five general EDA responses: 1) increased SCL, 2) reversal of the usual decline over time in SCL, 3) increased overall frequency of NS-SCRs, 4) increased frequency and magnitude of elicited SCRs, and 5) retarded rate of elicited SCR habituation (Dawson et al., 2000).

Chronic stimuli are defined as modulating increases and decreases in tonic arousal. There are three general types of chronic stimulus situations that will consistently magnify EDA. The first is the necessity of performing a task. In 1963, Lacey and colleagues found that in such situations, the anticipation and performance of practically any task will increase both SCL and the frequency of NS-SCRs, at least initially. Two competing explanations exist for the rise in SCLs in these situations: 1) tonic EDA could be related to a process of energy regulation, mobilization, or effortful allocation of attentional resources, or alternatively 2) using concepts such as stress, one can claim that tasks are challenging stressors, and a reliable physiological response to stressors is

increased sympathetic activation – and in particular, EDA arousal (Dawson et al., 2000). The second type of chronic stimulus situation involves social situations – here the concepts of stress and affect are particularly relevant and most often evoked. In a 1957 study, Dittes found that a psychotherapy patient's frequency of NS-SCRs were "inversely related to the judged permissiveness of the therapist" and thus concluded that EDA "reflects the anxiety of the patient, or his "mobilization against any cue threatening punishment by the therapist" (Dawson et al.,2000). It was proposed in a number of studies done by Dawson et al.(1983) as well as Nuechterlein & Dawson (1984) that patients exposed to high-expressed emotion (high-EE) (more critical) relatives should show heightened sympathetic arousal compared to patients exposed to low-expressed emotion (low-EE) (less critical) relatives. This prediction was tested by Tarrier et al. (1979), and the results indicate that the presence of high-EE and low-EE relatives do in fact have differential effects on EDA (Dawson et al., 2000).

c. Paradigm Three: Individual Difference

Lastly, in contrast to the preceding frameworks, the 'individual difference' paradigm starts from the premise that EDA is "a relatively stable subject trait related to behavioural and psychological individual differences" (Dawson et al., 2000). Drawing from the extant body of literature, two lines of evidence lend weight to the underlying assumption of the 'individual difference' paradigm. First, EDA components tend to exhibit moderate test-retest stability. Second, many EDA components have a partial genetic influence.

Individual variations in the rate of NS-SCRs and the rate of SCR habituation have been employed to define a trait called "electrodermal lability". Electrodermal labiles are defined as subjects who "show high rates of NS-SCRs and/or show slow SCR habituation, whereas electrodermal stabiles are those who show few NS-SCRs and/or fast

SCR habituation " (Dawson et al., 2000). Labiles differ from stabiles with respect to a host of psychophysiological variables, which include measures of both electrodermal and cardiovascular responsiveness (Dawson et al., 2000). Researchers studying behavioral differences concluded that "electrodermal activity is a personality variable that reflects individual differences in higher central processes involved in attending to and processing information" (Dawson et al., 2000). In this view, labiles should differ from stabiles in a variety of information processing tasks that, for example, may involve speed and vigilance. Studies that focus on behavioral and psychological variation with respect to this individual difference trait have shown that reliable abnormalities in electrodermal lability are associated with diagnosable psychopathology. In this group, the most common electrodermal abnormality is extreme stability in the form of very rapid habituation of the SCR orienting response (Dawson et al., 2000). With respect to schizophrenia patients, the most commonly reported EDA abnormality has been SCR non-responding and hyporesponding to innocuous tones. EDA findings focused on the study of schizophrenic patients have suggested "Tonic electrodermal hyperactivity may be not only an episode indicator but also an early precursor of symptomatic exacerbation or relapse in schizophrenia" (Dawson et al., 2000).

In summary, much of the research employing phasic and tonic EDA indices associated with schizophrenia in comparison to normal controls has been concerned with issues related to overall responsiveness to stimuli (including the SCR responder/nonresponder distinction) and overall arousal as indexed by SCL, respectively. Regarding indices related to attentional processes, a great deal of research has focused on phasic response habituation (e.g., decrease in SCR amplitude and magnitude as a function of stimulus repetition trials). Very little research has been performed on attentional

processes indexed by phasic responses to stimulus change (novelty) with schizophrenic subjects.

A repetition to cross-modal stimulus change preparation (e.g., a series of 15 tones followed by a light, and then another presentation of the original tone) with autonomic indices of orienting (phasic electrodermal and vasomotor responses) paradigm has been previously employed by some researchers (Furedy 1968; Morrison et al., 1996) in order to test Sokolovian accounts that posit a response decrease to repetition (habituation) and an increase to change (reinstatement) by reason, respectively, of confirmation and disconfirmation of a neuronal model of the about-to-be-presented stimulus. They also previously tested for the attentional effect referred to as "dishabituation" as defined already in terms of the same above phasic response measures. These tests generally confirmed all Sokolovian predictions except that for dishabituation in terms of phasic electrodermal response measures (Furedy, 1968, 1969; Morrison et al.,1996).

I.4. OBJECTIVES & HYPOTHESES

We have presented this cross-modal repetition-to-change preparation to normal controls and unmedicated patients with a diagnosis of schizophrenia while skin conductance activity was measured in order to examine the extent to which phasic electrodermal indices of orienting (attentional processes) would discriminate between clinical groups and normal controls. Additionally, possible influences of gender and laterality (bilateral recording in right-handed subjects) factors were examined.

We expected stimulus repetition and change to produce SCR decreases and increases, respectively, at least with normal controls. Based upon previous findings noted above, we hypothesized that schizophrenia patients as a group would show higher nonresponding rates and slower habituation during stimulus repetition compared to controls. Because previous research has suggested possible differences in SCR

habituation for schizophrenic electrodermal responders versus nonresponders (Gruzelier, 1973; Iacono, 1982), we tested these attentional effects (habitation, reinstatement, superinstatment & dihabituation) in responder subjects only from the two groups. The reason was to examine the attentional function, using a Skolovian paradigm, in schizophrenic responders only and to see if they differed from normal controls. Also we looked for any differential effects of laterality and gender in responder subjects only, and expected to see lower SCR in female patients (Zahn, 1981a).

II . Methods:

II.1 Participants

The research protocol described herein was reviewed and approved by the Ethics Review Committee, Alberta Hospital Edmonton. Following a complete description of the study to the participants, fully-informed consent was obtained prior to recording. Participants were told that they were free to discontinue testing at any time if they so wished. The procedures were noninvasive and unobtrusive. The auditory and visual stimuli presented were innocuous (neutral) and were of mild to moderate intensity.

Normal healthy controls: Sixty-eight volunteers (35 male, 33 female) (age: M = 26.6, SD = 7.4 years) were recruited by notices posted at community and hospital staff bulletin boards; the participants received pecuniary remuneration ($10) for participation in the study. Respondents who indicated a history of neurological disease, psychiatric illness, birth complications (e.g., anoxia), serious childhood illnesses (e.g., rheumatic fever), head trauma, or alcohol/drug abuse on a pretest interview form administered prior to the scheduling of test sessions were excluded from the study. Additionally, a computerized version of the Quick Diagnostic Interview Schedule III-R (Marcus et al., 1990) was administered after the recording session in a separate room, and participants who indicated clinically significant symptomatology in any areas on such were omitted from analysis.

Forty-seven patients (31 male, 16 female) meeting DSM-IV (American Psychiatric Association, 1994) criteria for a diagnosis of schizophrenia were examined

(age: M = 33.9, SD = 11.3 years). As a group, patients were in severe states of schizophrenic illness with both deficit negative symptoms and super-imposed florid symptomatology (first rank Schneiderian symptoms; Schneider, 1959).

All participants were clearly right-handed (Annett, 1970; Chapman and Chapman, 1987) and were naive with respect to the electrophysiological procedures. Participants were selected without regard to ethnicity, although ethnicity was recorded for possible future analysis if necessary, as some differences in absolute values related to ethnic origin for this variable have been reported in the literature (Boucsein, 1992). Participants were either free of neuroleptic medications, or recordings were obtained after discontinuation of all psychotropic medications for the appropriate washout periods, approximately 5 times their respective half-lives. Most schizophrenia patient participants were inpatients in a psychiatric assessment and treatment center specialised for severe psychopathology (Alberta Hospital Edmonton) at the time of recording. In all cases, the treating psychiatrist and a senior psychiatrist independently concurred on the diagnosis. The diagnosis was formed following careful review of patient history, symptoms observed during hospitalization/treatment, and clinical interviews. Seven (5 male, 2 female) schizophrenia group participants were outpatients at the time of testing.

Medications were discontinued/delayed as part of the present intake psychiatric assessment and diagnosis, which was performed only in cases where the treating psychiatrist was of the opinion that this action was sufficiently safe for each patient, that the patient's state was sufficiently stable in order to tolerate such, and that such was justifiable in order to permit accurate diagnosis. Diagnoses were in many cases often confirmed only later on in the course of treatment after psychophysiological and other psychiatric assessments were completed. Many of the same patients also had psychophysiological quantitative EEG assessment either later the same day or on a

different day following EDA recording. The experimenter was blind to provisional diagnosis at the time of EDA testing and data reduction.

The two groups differed significantly in age. The schizophrenics as a group were significantly older than the normal healthy controls, $t(113) = 4.22$, $p < .001$. The mean length of hospitalization prior to testing for schizophrenia patients was 17.8 (SD = 54.6) days (median = 7.0 days). The mean number of previous hospital admissions for schizophrenics was 0.5 (SD = 0.8), median = 0.0. Participants who showed no SCRs to stimuli presented on the initial 3 trials were classified as nonresponders (Bernstein et al., 1982).

II.2 Nonsignal Stimulus Preparation

The auditory stimulus consisted of a 2000-Hz, 72-dB SPL binaural tone delivered by matched headphones. The visual stimulus was a room illumination increase from the dimly-lit chamber background of < 0.1 lux to 108 lux by means of an overhead lamp directed at the wall in front of the participant, as measured with an illuminometer directed at the wall 214 cm in front of the participant at eye level. Stimulus duration (tone and light) was 300 ms. Stimulus intensity was established in earlier pilot studies with other hospital staff volunteers such that either stimulus elicited phasic electrodermal and vasomotor responses of comparable magnitude upon initial (trials 1-3) presentations.

A cross-modal nonsignal single stimulus repetition and dishabituation preparation (Furedy, 1968) was utilised in which, following 15 repetition (tone or light) trials, a cross-modal change trial (light or tone) was presented on trial 16, and a further repetition modality stimulus (tone or light) was presented on trial 17. Intertrial intervals were varied between 37, 45 (mean), and 53 s. Repetition stimulus modality was alternated across persons. After participants were seated in the test chamber and electrodes/sensors were attached, they were instructed that the study was concerned with measurement of

nervous system activity to simple tone and light stimuli which would be presented during the recording session. Participants were asked to rest with their eyes open and to avoid unnecessary movements during recording. Participants were instructed that no task was required in relation to the stimuli to be presented (i.e., nonsignal stimuli were utilised).

II.3 Apparatus and Recording Methods

Participants were seated in a padded armchair in a dimly-lit electrically shielded, sound-attenuated, air-conditioned chamber, maintained at a temperature between 22 to 24 °C. The recording equipment and the experimenter were located outside the test chamber. A high-resolution video camera positioned in the top left corner of the test chamber and a small video monitor located with the experimenter's apparatus provided continuous and clear visual contact with the participant during recording. Two-way auditory contact between the participant and experimenter was achieved with condenser microphones. The time(s) of movement and respiratory irregularities (e.g., cough, deep inspirations) during recording were noted by the experimenter for reference in subsequent offline raw data visual inspection and scoring.

Bilateral electrodermal activity was recorded with SensorMedics (Beckman) 8-mm diameter silver-silver chloride electrodes placed on the volar surfaces of the distal phalanges of digits III and IV of each hand, with constant voltage (0.6 V) skin conductance couplers. Electrode contact area was limited to approximately 0.7 cm^2 by use of double-sided adhesive collars. A 0.05 M NaCl in Unibase ointment mixture as recommended by Fowles et al. (1981) served as the electrolyte. Electrode bias potentials of each electrode pair were measured prior to each session to ensure bias potentials of < 500 μV, and random placement of electrodes across subjects was employed to prevent systematic polarization effects (Boucsein, 1992). Bilateral skin temperature was recorded

from the volar surfaces of the distal phalanges of digit V of each hand, with commercial temperature sensors affixed with surgical tape. Bilateral peripheral vasomotor activity (finger pulse amplitude) was measured from the volar surfaces of the distal phalanges of digit II of each hand with commercial photoplethysmograph amplifiers (AC coupling), but was not analyzed for the present study. Respiration was recorded from a strain gauge placed around the subject's chest with a bridge amplifier on a separate channel and was employed to aid in the detection and exclusion of respiratory or movement artefact during offline visual inspection and scoring of dependent measures. Stimulus onset/offset was recorded on a separate event channel. The analogue output from couplers was continuously digitized at a rate of 40 Hz, and channels were displayed in real time on the experimenter's computer monitor during recording. Integrated hardware/software commercial instrumentation (Precision Instruments, Inc.) and a microcomputer were employed for experimental control of stimuli, timing, and recording of dependent physiological measures. Data reduction was performed offline with custom-written software, which permitted full visual inspection of the records and corrections for machine-scoring errors.

II.4 Dependent Measures

Skin conductance increases ≥ 0.05 μS initiated 1 to 4 s poststimulus onset were scored as phasic responses (SCRs). A square root transform was applied to the SCR data prior to analysis to reduce the skewness associated with small responses. Mean prestimulus skin conductance levels (SCL) for the 5-s period preceding stimulus onset for each trial and from 40 to 45 s post-trial 17 were scored as tonic electrodermal measures. Mean prestimulus skin temperature levels (STL) were obtained for 5 s prior to stimulus onset for each trial as an index of tonic peripheral vasomotor activity.

II.5 Statistical Analysis and Experimental Design

The 0.05 significance level was adopted for all analyses. The SCR data were examined with mixed analyses of variance (ANOVAs). Between-subjects factors were Group, Gender, and Repetition Stimulus Modality (light; tone), with Laterality (left; right hand recordings) and Trials as within-subjects factors. Analyses involving repeated measures factors utilised Greenhouse-Geisser corrections to the degrees of freedom where appropriate, with corrected probability values reported.

The following issues (effects) were examined:

1. Overall responsivity for all subjects for trials 1-17 was examined with a 5-factor ANOVA. Between-subjects factors were Group, Sex, and Repetition Stimulus Modality (light or tone). Within subjects factors were Laterality (left-hand; right-hand recordings), and Trials. A primary question to be examined was whether a significant main effect of Group would emerge from this analysis. The main effect of Trials and possible interactive effects involving the Trials factor were also examined. Overall responsivity for all subjects for trials 1-17 was also examined with a 4-factor ANOVA calculated for total response frequency.

2. Overall responsivity for SCR responders only. The same 5-factor AVOVA as described above was performed for responders only for trials 1-17. The 'no-response' for the initial 3 trials definition of nonresponders (Bernstein et al, 1982) was utilized. Main and possible interactive effects involving the Trials factor were also investigated.

The remaining analyses for cognitive attentional effects to be noted below were performed for SCR responders only, in order to avoid complications with interpretation

related to the fact that a higher proportion of patients were electrodermal nonresponders than were normal controls. The following four discrete cognitive attentional effects which are clearly derivable from Sokolovian Orienting Response Theory were then examined separately with 5-factor ANOVAs:

3. Habituation ANOVA (decline in response magnitude as a function of stimulus repetition during trials 1 to 15).

4. Reinstatement ANOVA (response to the cross-modal stimulus change on trial 16 exceeding the response to the final repetition modality stimulus on trial 15).

5. Super Reinstatement ANOVA (response to novel cross-modal stimulus change on trial 16 exceeding the response to the initial novel stimulus on trial 1).

6. Dishabituation ANOVA (increased response to repetition modality stimulus following inter-modal stimulus change compared to the response to the immediately preceding repetition modality stimulus).

For each of the above four discrete attentional effects analysis, primary questions to be examined included whether the main effect of Trial would be evident, which would indicate whether or not the attentional effect itself clearly emerged, and if so, whether interactive effects involving factors such as Group by Trial, or Group by Gender by Trial would emerge in these analyses.

III. RESULTS:

III.1 Overall Responsivity (trials 1 to 17)

SCR Magnitude: The five factor ANOVA (Group X Gender X Modality X Trials X Laterality) performed to assess overall responsivity as indexed by mean SCR magnitude for all subjects for trials 1 to 17 yielded a significant main effect of Group $F(1,107) = 4.82$, $p = 0.03$, which indicates that the schizophrenics had significantly reduced overall responsivity compared to normal controls, as depicted in Figure 1. A highly significant main effect of Trials also occurred in this analysis [$F (16,1712)=56.76$, $p <. 001$, epsilon = .452], indexing a decline across groups in mean phasic response magnitude as a function of repetition trials 1-15 (i.e., phasic response habituation), followed by a clear increase to stimulus novelty (stimulus change) across groups on trial 16 (i.e., an effect of orienting response reinstatement). See Figure 1.

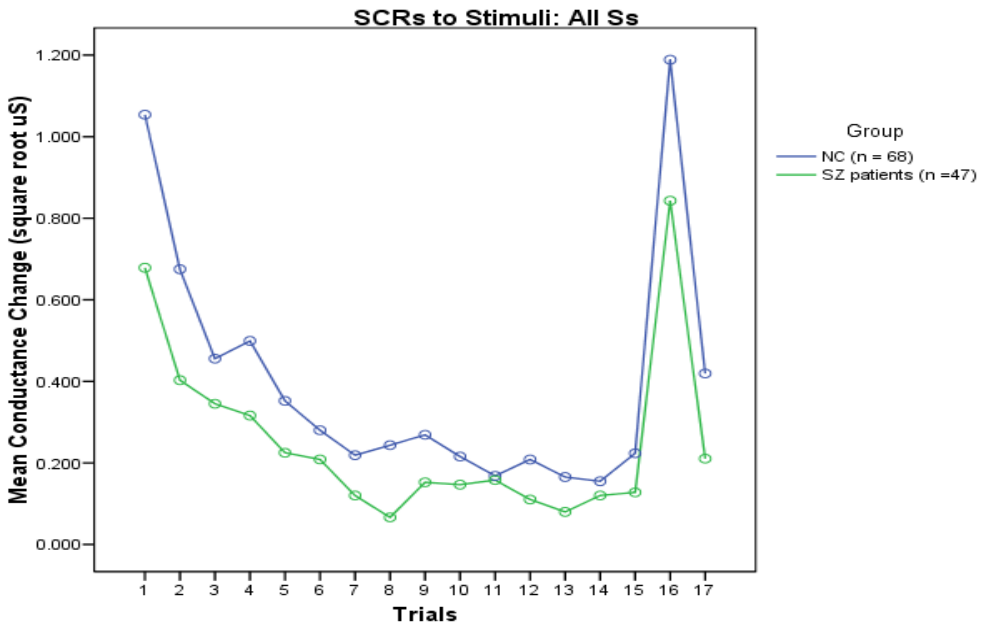

Figure 1: Mean skin conductance response (SCR) change for the Group by Trials functions for trials 1-17 for all subjects. N = 68 normal controls (NC) and N = 47 schizophrenia (SZ) patients.

With the exception of a significant Group X Trials interaction [F (16,1712)=2.25, p=. 027, epsilon (ε)=. 452], no other significant main effects or interactions resulted from this analysis. Regarding the Group X Trials interaction, normal controls showed a greater reaction to the initial stimulus and to the cross-modal change stimulus than did schizophrenics, whereas less difference between groups was evident during the middle to later portion of the repetition series (see Figure 1).

Response Frequency: The 5-factor ANOVA calculated for total SCR frequency scores for all subjects for all trials revealed that the schizophrenics showed significantly fewer stimulus-elicited responses then did the normal controls, F(1,107) = 5.83, p = .017, for the main effect of Group (means of 4.79 and 7.01 SCRs for schizophrenics and normal controls, respectively). Male normal controls displayed more SCRs than female normal controls, whereas female schizophrenics showed more SCRs than male

schizophrenics, which produced a significant interaction of Group and Sex, $F = 4.42$, $p = .038$. No other significant main or interactive effects resulted from this analysis, including the factor of Laterality (left/right hand recordings).

Responders: The same five-factor ANOVA as described above performed for SCR magnitude to index overall responsivity for SCR responders (response to trials 1 to 3 definition) only for trials 1 to 17 did not reveal a significant main effect of Group, $F < 1$ (see Figure 2).

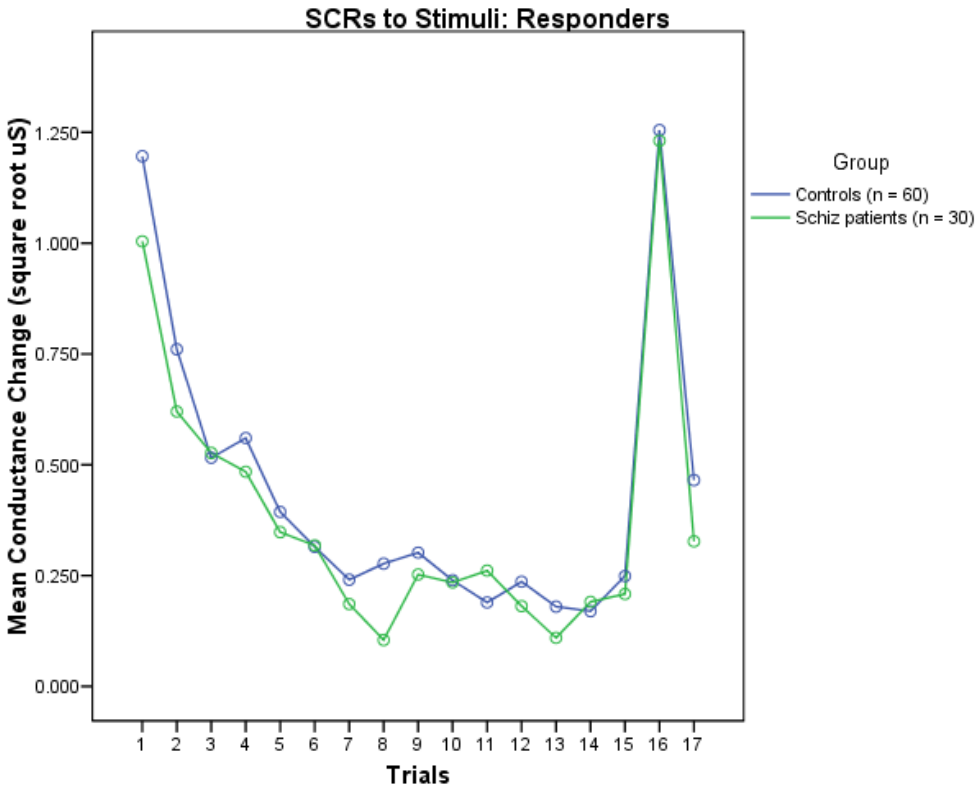

Figure 2: Mean skin conductance response (SCR) change for the Group by Trials functions for trials 1-17 for Responders only. N = 60 normal controls and N = 30 schizophrenia patients.

A higher proportion of the schizophrenic group were nonresponders (36%, 17 subjects) as compared to the normal control group (12%, 8 subjects). See Tables 1 and 2.

Table 2: Demographic characteristics of patients and controls (all subjects).

		Schizophrenic Patients	Normal Controls
Sample size (n)		47	68
Age –mean (years)		33.89	26.56
Gender	Male	31	35
	Female	16	33

Table 3: Demographic characteristics of patient and controls (Responders only).

		Schizophrenia Patients	Normal Controls
Number		30	60
Gender	Male	19	32
	Female	11	28

III.2 Cognitive Attentional Effects (Responders only)

Habituation (trials 1 to 15) ANCOVA with age as covariate: A highly significant decline in response strength was evident across groups during the stimulus repetition series [$F(14,1134) = 8.40$, $p < .001$, epsilon = .595], for the main effect of Trials [linear

$F(1,81) = 22.55$, $p < .001$], indicating that a very clear effect of orienting response habituation (decline in response magnitude as a function of stimulus repetition) was evident. This effect did not vary as a function of group or group and gender, $Fs < 1$ for the Group X Trials and Group X Sex X Trials interactions.

Habituation (trials 1 to 15) ANOVA: A highly significant attenuation in responsivity was evident across groups as a function of stimulus repetition, $F(14,1148) = 42.37$, $p < .001$, epsilon = .592, for the main effect of Trials (linear $F(1,82) = 42.37$, $p < .001$), which indicates that habituation clearly occurred. This effect did not differ as a function of group or group and gender ($Fs < 1$ for the Group X Trials and Group X Sex X Trials interactions).

With the exception of a significant Sex X Trials interaction, $F(14,1148) = 1.93$, $p < .05$, which was related to the fact that females showed a higher reaction than males to the initial (trial 1) stimulus and females displayed a lower reaction than did males to later repetition series trials, no other significant main or interactive effects resulted from these analyses.

Habituation (trial 1 & trial 15) ANOVA: A highly significant main effect of Trial resulted across groups, $F(1,82) = 213.23$, $p < .001$, again confirming the very strong effect of habituation across groups from the initial stimulus to the final repetition series stimulus. Similar to the outcome for the trials 1 to 15 ANOVA reported above, a significant Sex X Trials interaction resulted, $F = 11.83$, $p < .001$. The latter interaction was due to the fact that females displayed a higher reaction to the initial stimulus than males, and females showed a lower reaction to the final repetition stimulus compared to males.

Re-instatement (trial 15 and trial 16) ANOVA: A very clear effect of orienting response reinstatement emerged (response to cross-modal stimulus change on trial 16 markedly exceeding the response to the final repetition modality stimulus on trial 15), $F = 141.92$, $p < .001$, for the main effect of Trial. The effect of reinstatement was uniform across groups, $Fs < 1$ for the Group X Trial and for the Group X Sex X Trial interactions.

Super Reinstatement (trial 1 and trial 16) ANOVA: The effect of super reinstatement (response to novel cross-modal stimulus change on trial 16 exceeding the response to the initial novel stimulus on trial 1) approached significance, $F = 3.17$, $p = .079$, for the main effect of Trial, with a somewhat higher mean response found for trial 16 as compared to trial 15 across groups.

Thus, a non-significant trend in the expected direction was seen. This outcome was not modulated by an interaction with the factor of Group, nor by the factors of Group and Sex, $Fs < 1$ for the Group X Trial and for the Group X Sex X Trial interactions. No other significant main or interactive effects resulted from this ANOVA.

Dishabituation (trial 15 and trial 17) ANOVA: Orienting response dishabituation (increased response to repetition modality stimulus following inter-modal stimulus change compared to the response to the immediately preceding repetition modality stimulus) was clearly evident across groups, $F = 9.62$, $p < .003$, for the main effect of Trial. No other significant main or interactive effects emerged in this analysis.

It is worthy to note that ANCOVAs with age as the covariate performed for the other three discrete attentional effects of reinstatement, super reinstatement, and dishabituation revealed essentially the same outcomes, as did the ANOVAs reported above.

IV DISCUSSION

In this study we used a cross-modal repetition-to-change orienting paradigm comprising 15 repetition (light, or tone) trials, a cross-modal change trial (tone or light), and a repeated, "dishabituation" (light or tone) trial to examine possible attentional abnormalities in unmedicated schizophrenia patients.

Overall responsivity as indexed by mean SCR magnitude for all subjects for trials 1 to 17 yielded a significant main effect of Group, which indicates that that schizophrenic patients had significantly reduced overall responsivity compared to normal controls. A highly significant main effect of Trials also occurred in this analysis, indexing a decline across groups in mean phasic response magnitude as a function of repetition trials 1-15 (i.e., phasic response habituation), followed by a clear increase to stimulus novelty (stimulus change) across groups on trial 16 (i.e., an effect of OR reinstatement) which is consistent with the Sokolovian paradigm of OR in both groups.

We found a higher proportion of 36% (17 subjects) of the schizophrenic group were nonresponders as compared to the normal control group (12%, 8 subjects). These findings are in good agreement with those reported in the literature (40% nonresponders in schizophrenic subjects versus 10% for normal control subjects) (Ohman, 1981).

The four cognitive attentional effects, which were performed only for SCR responders, did not show significant differences between the schizophrenic subjects and the normal controls. From this we can conclude that there was no attentional impairment in unmedicated schizophrenic subjects and normal controls using the Sokolovian skin

conductance orienting system (SCOR) habituation paradigm and also using the cross modal repetition to change paradigm.

Furedy (1993) argues that the habituation-to-repetition phenomenon does not appear to be restricted to weak stimuli as even with loud noises and shocks SCR habituation also occurs to these stimuli. Thus, the usual strategy of administering moderate tones and simply labeling the elicited SCRs as ORs may reflect, for example, simple reactivity. He also argues that disconfirmatory stimulus (cross-modal, tone/light or light/tone) change of the cognitive Sokolovian sort is neither sufficient nor necessary for producing an SCR increase (Furedy and Scull 1971). He proposed to actually measure the OR-like properties of these responses, and compare individuals in terms of these properties. Two of the OR-like properties, habituation and increase to change (reinstatement) in addition to a third effect which is the super-reinstatement effect, wherein the 16th change trial produces greater electrodermal responding than the initial 1st repetition, are more consistent with the Skolovian neuronal model notion (Furedy, 1993). Thus, it would be better to differentiate these three attentional OR-like properties so EDA would likely to be a more discriminating psychophysiological investigatory tool of the important psychological process of attention.

Our findings were consistent with the Skolovian habituation paradigm in responders in both groups and also were consistent with the other two effects (reinstatement and super-reinstatment). However, they did not differ between responders in schizophrenic subjects compared to normal controls. The dishabituation attentional effect, which is clearly able to be derived from Sokolov's theory of OR (1963) was also examined and was evident in both groups.

Flor-Henry & J. Morrison (personal communication) used the same repetition and cross-modal Change model to study those four effects using the SCL index. Unique

impairments were found in SCL with respect to habituation, reinstatement, and dishabituation in relation to mild nonsignal stimuli for male schizophrenics, which has not been reported previously. However, in our study those impairments were not observed.

The laterality effect was absent in this study, which is congruent with some previous research with schizophrenic patients (Iacono, 1982; Iacono et al., 1983; Iacono and Tuason, 1983), but is incongruent with other research (e.g., Gruzelier, 1973) and suggests that the question of laterality effects with schizophrenics remains to be resolved.

Because unmedicated patient were studied, present findings indicate that medication effects alone can not be responsible for the phasic response hyporeactivity found n SCZ is significantly related to features of the illness itself. Our findings consolidate the evidence regarding the presence of two distinct populations of SCZ patients based on SCOR research findings. One is the Rs who seem to have intact OR and attentional capacity and the NRs who do not have intact OR and attentional capacity. This seems to be consistent with clinical classification of the psychotic symptoms to positive and negative symptoms, where Rs tend to show positive symptoms and NR show more negative symptoms. These finding could be helpful clinically to optimize treatment, which will be discussed in the following section.

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VII. Concluding Remarks

The cross-modal orienting response dishabituation paradigm which was used to study OR in schizophrenics versus normal controls showed similar rates of nonresponse as reported in the literature. In all responders, the four attentional effects (habituation, reinstatement, super-reinstatement, dishabituation) were evident and did not show significant differences between the schizophrenic subjects and the normal controls. There was no evidence of any laterality effect or any gender-specific differences.

Because unmedicated patients were studied, the present findings indicate that medication effects alone can not be responsible for the phasic response hyporeactivity found in schizophrenics and that these effects are significantly related to features of the illness itself. Our findings consolidate the evidence regarding the presence of two distinct populations of schizophrenic patients based on SCOR research findings. The responders seem to have intact OR and attentional capacity and the nonresponders do not have intact OR and attentional capacity. This seems to be consistent with clinical classification of the psychotic symptoms to positive and negative symptoms, where responders tend to show positive symptoms and nonresponders show more negative symptoms.

These findings could be helpful clinically to optimize treatment. It is known that schizophrenic subjects with negative symptoms have a worse prognosis and tend to be treatment-resistant. Thus, clozapine could be considered earlier in treatment for nonresponders instead of waiting to try different antipsychotics. Trying augmenting strategies like ECT earlier in treatment is another possibility. For the responders, augmenting medications like propranolol aimed at reducing the sympathetic drive could be useful strategy. We know that the longer psychoses are untreated, the worse the

prognosis is, and choosing an effective treatment plan is of paramount importance in determining the prognosis of the illness.

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