Event-related potential correlates of theory of mind in schizophrenia

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Abstract

Theory of mind (ToM) is the knowledge that other people have minds, thoughts, beliefs and values different from our own. Patients with schizophrenia are generally thought to be impaired at tasks requiring this ability. Frith (1992) has proposed that specific signs and symptoms of schizophrenia are associated with dysfunction in ToM ability. The purpose of the present study was to investigate the role of thought disorder in theory of mind and to tease out the electrophysiological correlates of this phenomenon. Participants partook in an intention attribution task, during which event-related potentials (ERPs) were recorded. Patients with high ratings of thought disorder performed worse than those with low thought disorder and significantly worse than normal subjects. ERP results were unexpected as no differences were detected for ERPs on frontal sites. A significant difference in the P600 component was observed on Pz. Possible explanations for parietal activation are discussed.

Résumé

La théorie de l'esprit (TE) se dit du fait d'être conscient que d'autres personnes ont des esprits, pensées, croyances et valeurs différentes des nôtres. Il est généralement cru que les patients atteints de schizophrénie sont désavantagés dans la performance de tâches requérant cette aptitude. Frith (1992) a proposé que des signes et symptômes spécifiques à la schizophrénie soient associés avec les dysfonctions dans les aptitudes de la TE. Le but de la présente étude est d'examiner le rôle du trouble de la pensée dans la théorie de l'esprit et de trouver les corrélats électrophysiologiques de ce phénomène. Les participants ont pris part à une tâche d'attribution d'intention durant laquelle des potentiels évoqués (PEs) reliés aux événements étaient enregistrés. La performance des patients dont le niveau de trouble de l'esprit est élevé était inférieure à celle des patients dont le niveau d trouble de l'esprit est bas et significativement inférieure à celle des sujets normaux. Les résultats des PEs étaient inattendus puisqu'aucune différence n'était détectée pour les PEs sur le lobe frontal. Une différence significative dans le composant P600 était observée sur Pz. Des explications possibles pour l'activation pariétale sont traitées.

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Introduction

<u>Schizophrenia</u>

Schizophrenia is one of the most complex and fascinating mental disorders. The symptoms of this disease have been documented for well over a hundred years, beginning with Kraepelin's description of "dementia praecox" in the late 19th century (Rosenzweig, Leiman and Breedlove, 1996). Observations over the years have resulted in a comprehensive list of characteristics which medical health professionals can use to diagnose the disorder. In fact, the Diagnostic and Statistical Manual of Mental Disorders (the clinicians' guide for diagnosing mental disorders) requires that individuals have at least two of the following criteria for the better part of one month if they are to achieve a diagnosis of schizophrenia: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour and negative symptoms (American Psychiatric Association, 2000; Zuckerman, 1999). This consistent symptom profile is not only critical for diagnosis, but may aid in understanding the etiology of this disease.

Symptoms and Etiology

While modern science is years away from wholly understanding the disease of schizophrenia, insight into the neurological basis of these symptoms brings us much closer to this goal. A significant obstacle in schizophrenia research involves the integration of discoveries about the psychological, neurophysiological and neuroanatomical aspects of the disease. With so many unknowns surrounding schizophrenia, utilizing consistent features such as schizophrenia symptoms provides the opportunity to formulate hypotheses as to the fundamental deficits in the disease. For example, there is extensive literature reporting memory deficits, cognitive impairments, social interaction deficits and problems with decision making (Gooding and Tallent, 2004; Heydebrand et. al, 2004; Pillmann, Bloink, Balzuweit, Haring and Marneros, 2003; Hutton et al., 2002). Knowledge of the neural underpinnings of these processes allows for an integrated interpretation of symptom profiles as well as the increased ability to deduce theories pertaining to the etiology of schizophrenia. Subsequently, a growing area of interest is that of social cognition and schizophrenia.

Social Cognition

Social cognition refers to the "processes and functions that allow a person to understand and benefit from the interpersonal world," (Corrigan and Penn, 2001). It is the interface between neurocognitive abilities and social situations and is comprised of many components including the ability to perceive emotion in others, to infer what others are thinking and to understand the rules that govern social interactions (Green, 2001). Theory of mind (ToM) engages a subset of social cognition abilities and this study aims to investigate the basis of ToM deficits in people with schizophrenia.

Theory of Mind

Theory of mind refers to one's knowledge of other's thoughts, beliefs, hopes, intentions and desires (Baron-Cohen, 1994). Moreover, it includes the ability to use this knowledge to interpret and predict the intentions and behaviours of others. The expression "theory of mind" was created by Premack and Woodruff (1978) who investigated awareness of independent thoughts and/or beliefs in chimpanzees; i.e. whether or not chimpanzees know different individuals have different thoughts and beliefs, and whether they can use this knowledge to predict an individual's behaviour. In one of their tasks a chimpanzee watched a video of a man trying to access an out-of-reach object. Premack and Woodruff asserted the chimpanzee proved the ability to understand intentions because she subsequently chose a picture which logically solved the man's problem, instead of an unrelated image (Premack and Woodruff, 1978; Novak and Pelaez, 2004). This study laid the groundwork for further ToM research in the human population.

Literature reports the human child develops ToM ability around four years of age (Wimmer and Perner, 1983). Throughout one's lifetime, ToM faculties are constantly enlisted and the ability to infer another's intention and/or predict subsequent behaviour is honed with time. It should be noted that the terms mentalize and metarepresentation are often used interchangeably to refer to theory of mind ability.

Assessing Theory of Mind Ability

Researchers have had to develop a number of tools with which to test mentalizing ability. Dennett (1978) suggests the only accurate way to assess ToM is to measure the ability to predict behaviour based on a false belief. Simply predicting actions based on actual fact is not indicative of an intact ToM, as one's response could be based on the true conditions of the situation rather than the ability to have an assumption based on what is known of another's mental state. Consequently, various researchers have devised a number of theory of mind tests. As research on this phenomenon arose from the understanding of the development of the mind of the human child, many such tasks are directed towards this population.

False Belief Tasks

Wimmer and Perner (1983) devised the "Sally-Ann task," a false-belief task in which a child is presented with two dolls (Sally and Ann), one with a basket and the other with a box. Sally is shown to put a marble in her basket and then she leaves the room. Ann then moves the marble from Sally's basket to her box. When Sally returns to the room, the child is asked, "Where will Sally look for her marble?" A child with theory of mind will answer correctly; Sally will look in her basket. One without a ToM will say that Sally will look in the box; the actual location of the marble (Wimmer and Perner, 1983). Variations on this task require a child to inquire about another individual's thoughts as opposed to their actions.

In the "Smarties" task, a child is shown a Smarties box and asked what is inside (Perner, Frith, Leslie and Leekam, 1989). The child, of course, answers "Smarties," or "candy." The child is then shown that the box has no Smarties but, instead, a pencil. He/she is then asked what another child will think when he/she is shown the box for the first time. A subject will pass this test if he/she realizes that the new child will have a false belief, i.e. that the box contains Smarties. These tasks highlight an important categorization in ToM tasks, that of first- and second-order mental states.

First- and Second-Order Tasks

First-order false belief tasks demand the subject to comprehend a characters' belief about the world (e.g. Where does she think the marble is?). A second-order task, however, engages more complex theory of mind skills and requires the subject's awareness of a character's beliefs about the beliefs of another character (e.g. Where does she think John thinks the marble is?) (Happe,1995).

Theory of Mind in Adults

The research paradigms described are necessarily simplistic and, consequently, more demanding and naturalistic tasks have been developed especially for the assessment of mentalizing ability in adults. Happe (1994) designed a collection of short stories relating to the motivation behind expressions made in everyday speech which may or may not be taken literally. For example, you are asked to provide an opinion on someone's new hairstyle. You think the hairdo is repulsive but you could respond that it is fine for any number of reasons (i.e. to spare his/her feelings, to be sarcastic or funny, or to convince the individual to go out in public and humiliate themselves further) (Happe, 1995). The meaning in Happe's stories is meant to be explicit, such that a single interpretation can be made by a subject with intact ToM. Happe created stories to be categorized under 12 headings: Lie, White Lie, Joke, Pretend, Misunderstanding, Persuade, Appearance/Reality, Figure of Speech, Irony, Forget Double Bluff and Contrary Emotions (Happe, 1994). An example of an Irony story follows:

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Ann's mother has spent a long time cooking Ann's favorite meal; fish and chips. But when she brings it in to Ann, she is watching TV, and she doesn't even look up, or say "Thank you." Ann's mother is [angry] and says, "Well that's very nice, isn't it! That's what I call politeness!" (p. 78)

In response to this story, a subject would be asked, "Is it true, what Ann's mother says?" and, "Why does Ann's mother say this?" Other tasks present similar story lines and ask the subject to explain the meaning behind the actions or statements of characters in the stories (Corcoran, Mercer and Frith, 1995; Calarge, Andreasen and O'Leary, 2003).

These tests exemplify the types of tools available to assess the ToM ability in adults. They tap the subtleties of the mentalizing process through the presentation of naturalistic situations. A major draw-back of many of these tasks, however, is their extensive verbal nature. To read and comprehend these stories necessarily relies on cognitive processes, such as working memory. Researchers working with patient populations (e.g. patients with schizophrenia) concede cognitive impairments in their subjects and it follows that this cognitive delay would impair the ability to process ToM-type stories. Thus, investigators are constantly devising new tasks which require less accessory cognitive abilities in an effort to isolate ToM processes. For example, Heavey, Philips, Baron-Cohen and Rutter (2000) endeavored to create a more ecologically-valid ToM test. The "Awkward Moments" task is a compilation of clips from British television commercials and television advertisements; each clip depicting a character in a socially awkward or unpleasant situation. Subjects are required to respond to questions about the clip for which an accurate response would not only require understanding of the

character's beliefs about the situation but also of the social implications of the character's actions (Heavey et al., 2000).

Theory of Mind and Schizophrenia

ToM impairments in schizophrenia – irrespective of the task – are robust and supported by a growing literature (Hardy-Bayle, Safarti and Passerieux, 2003; Pickup and Frith, 2001; Sarfati, Hardy-Bayle, Brunet and Widlocher, 1999; Doody, Gotz, Johnstone, Frith and Owens, 1998; Corcoran, Mercer and Frith, 1995). Corcoran et. al, (1995) engaged subjects in a task which assessed their ability to decipher the meaning behind veiled speech. Subjects had an interaction between two characters read aloud to them. The passage concluded with one of the characters dropping an obvious hint to the other. The subject's task is to describe what was really meant by the hint. An example follows:

Paul has to go to an interview and he's running late. While he's cleaning his shoes, he says to his wife, Jane, "I want to wear that blue shirt, but it is very creased."

Question: What does Paul really mean when he says this? (Corcoran et al., 1995) Compared with age-, sex-, education-, and occupation-matched controls, schizophrenic patients exhibited impaired performance on this Hinting task. Pilowsky, Yirmiya, Arbelle and Moses (2000) investigated ToM abilities in children and adolescents diagnosed with schizophrenia. Performance on a false-belief task was less accurate for subjects diagnosed with schizophrenia than for normal control subjects. Doody et al. (1998) administered first- and second-order ToM tasks to various groups of subjects in an attempt to measure the impact of IQ on performance on ToM tasks. Schizophrenic patients and subjects with mild learning disorder initially proved to be impaired on second-order ToM tasks. When comprehension of the task was controlled for, however, analysis revealed a deficit only for schizophrenic patients. Corcoran and Frith (2003) also presented subjects with first- and second-order theory of mind stories. Compared to normal control subjects, patients with schizophrenia displayed difficulty understanding the intention behind indirect speech as well as poor appreciation for situations involving deception and false-beliefs.

Frith's Theory

Clearly, the patient with schizophrenia has insufficient ToM capabilities. The question remains as to where the nature of this ToM deficit lies; does the disease, schizophrenia, diminish an individual's ToM abilities or vice versa? It is inevitably ambitious to tackle this question entirely, but an appropriate place to begin is by linking knowledge of ToM processes to symptoms of schizophrenia. Consequently, Frith (1992) has used a social cognition model to create a hypothesis to explain the overt symptoms associated with schizophrenia. Frith's theory describes a fundamental deficit within a system that is supposed to function by recognizing and monitoring one's own willed intentions in addition to attributing intentions, thoughts and beliefs to other individuals. In fact, Frith highlighted three aspects of metarepresentational dysfunction which are thought to underlie the signs and symptoms of schizophrenia. These are: awareness of our own goals, awareness of our own intentions and awareness of the intentions of others. He hypothesized: 1) that lacking awareness of goals results in a poverty of will and thus negative and positive behavioural abnormalities, 2) that an unawareness of one's own

intentions will lead to a lack of self-monitoring resulting in abnormalities in the experience of action, and 3) that deficient awareness of other's intentions can lead to delusions of persecution and disorganization (Frith, 1992; Corcoran, 2000).

The hallmark of Frith's theory, thus, is his argument that specific signs and symptoms reflect the precise nature of the ToM failure. For example, negative symptoms are posited to reflect an initial and pervasive breakdown in the ability to represent intentional behaviour resulting in abulia (or lack of will), alogia (poverty of speech), athymia (blunted or flat affect), poverty of action and/or inappropriate action (Frith, 1992). Paranoid delusions were hypothesized to arise from a disruption in the system that prevents the accurate representation of other's thoughts and beliefs. Delusions of control and auditory hallucinations – also referred to as passivity phenomenon – are thought to be the effect of an inability to monitor one's own intentions to act. Formal thought disorder is said to reflect the inability to represent and/or consider the state of knowledge of another person; for example, a thought-disordered speaker's tendency to name people or objects as *he, she or it* without first introducing them to the listener (Corocoran, 2001).

Support for Frith's Theory

Frith's hypothesis was tested in a series of studies with schizophrenic patients (Corcoran et al., 1995; Frith and Corcoran, 1996; Corcoran, Cahill and Frith, 1997; Pickup and Frith 2001). Six mutually exclusive subgroups were created to isolate the main signs and symptoms in Frith's theory: 1) Negative Signs; patients displaying negative behavioural signs, 2) Positive Signs; patients with formal thought disorder and

disorganized behaviour, 3) Paranoid Delusion; patients with paranoid-type delusions, but without behavioural signs, 4) Passivity Features; patients presenting with passivity phenomenoa (i.e. delusions of control, thought insertion, thought withdrawal, second person auditory hallucinations), 5) Other Symptoms; patients who presented primarily with other less common symptoms and displayed none of the common symptoms and 6) Remission; patients with a diagnosis of schizophrenia but whose symptoms had been in remission for at least two weeks. In line with Frith's predictions, it was expected that performance would be impaired on ToM tasks specifically in patients with formal thought disorder, negative symptoms and paranoid-type delusions. Results supporting this hypothesis were obtained. Corcoran et al. (1995) demonstrated that patients with thought disorder, negative features, and paranoid delusions scored lower on a ToM task aimed at assessing the ability to understand hints, than the other symptom subgroups and normal controls. Frith and Corcoran (1996) assessed the ToM abilities of symptomatic schizophrenic patients. Each subject listened to stories while viewing cartoon depictions of the events in each story. Subjects were subsequently required to answer two questions: one memory question about the story (a control measure) and one ToM question, gauging the subject's ability to infer the mental state of a character in the story. Results were in accordance with Frith's theory, i.e. patients with behavioural signs were impaired on the task, while those with passivity phenomena performed similarly to normal controls. Pickup and Frith (2001) made further attempts to tease out a symptom/ToM association. Subjects completed first- and second-order false belief tasks and their performance was analyzed using regression methods. In this study, schizophrenic patients were impaired on second-order tasks only. The analysis revealed

patients with many positive and negative behavioural signs were impaired on ToM tasks as compared to normal controls. Interestingly, patients whose symptoms were in remission performed as well as normal controls.

Research from other laboratories also highlights psychotic symptoms associated with a deficit in mentalizing ability. Sarfati, Hardy-Bayle, Brunet and Widlocher (1999) employed a predominantly non-verbal task to assess ToM ability in schizophrenics. Subjects were presented with a series of comic strips and asked to complete them by selecting the correct answer card. In the first condition the answer cards were pictures and in the second, written phrases. Schizophrenic patients with primarily disorganization characteristics performed poorly on both the verbal and non-verbal task as compared with normal, depressed, and non-disorganized schizophrenic controls (Sarfati et al., 1999). In a study using a similar non-verbal comic strip task, subjects were asked to explain the behaviour of characters presented in the comic strips. Schizophrenic patients with thought and speech disorganization were poorer at attributing mental states to others and based their interpretations not on mental states, but on the frequency of the behaviour displayed (Safarti and Hardy-Bayle, 1999). Langdon, Coltheart, Ward and Catts (2004) found high error rates on a false-belief picture sequencing task were associated with ratings of positive formal thought disorder. Greig, Bryson and Bell (2004) also suggest poor ToM ability in patients with schizophrenia is related to thought disorder and cognitive disorganization. These researchers assessed ToM and revealed performance varied according to schizophrenic diagnosis; i.e. disorganized patients scored more poorly than non-disorganized patients. Measures of thought disorder and verbal memory

used in this study were analyzed and found to account for 30% of the variance in ToM scores (Greig et al., 2004).

Localizing Theory of Mind Ability

With an established link in place, it is necessary to consider where these processes are localized in the brain. Theory of mind is considered among the higher-order cognitive functions and the prefrontal cortex is known to contribute to these cognitive processes specific to humans (Baron-Cohen, 1994). Necessarily complex, the process requires the integration and amalgamation of both basic (e.g. visual identification and recognition) and complex (e.g. emotion recognition, knowledge integration) procedures. Subsequently, many executive functions have been localized to frontal areas and this trend is maintained in a good portion of theory of mind research.

Imaging Studies

Pioneering studies by Baron-Cohen et al. (1994) implicated frontal areas in ToM processing. Using single photon emission computerized tomography (SPECT) they hypothesized that adult participants performing a mental state recognition task would have significant orbito-frontal activation. Compared to normal control subjects, schizophrenic patients did indeed display increased cerebral blood flow in the right orbito-frontal region. Brunet, Sarfati, Hardy-Bayle and Decety (2000) employed a nonverbal task to investigate subjects' ability to attribute intention to others. Healthy subjects were presented with a series of comic strips depicting stories in sequential order. The task was to choose which of the three answer choices concludes the cartoon story.

Three types of comic strip stories were presented, one requiring attribution of intention and two control conditions (involving only physical logic). Positron emission tomography (PET) scans revealed an increase in cerebral blood flow to the right medial prefrontal cortex in subjects engaged in tasks involving attribution of intention (Brunet et al., 2000). Fletcher et al. (1995) observed cerebral activity (through PET) during a story comprehension task. Subjects were presented with three story conditions; one story required the attribution of mental states and thus targeted theory of mind ability, the other control conditions were paragraphs of unrelated sentences and stories about the physical properties of objects. Their study evidenced a significant medial frontal activation across the left hemisphere during the ToM task. Another PET study tapped ToM ability by asking subjects to produce a narrative about the mental state of a theoretical person they might meet in a park. As compared to the control condition (in which subjects simply read a non-ToM passage aloud) the ToM task resulted in medial frontal activation (Calarge et al., 2003). Russell et al. (2000) engaged schizophrenic subjects and normal controls in the "eyes" task, which requires subjects to choose which of two words illustrates the intention in photographs of pairs of eyes. Patients with schizophrenia made more errors on this task and, using functional magnetic resonance imaging (fMRI), they were reported to have a lower blood-oxygen level dependent signal in the left inferior frontal gyrus than normal controls. Based on reports from the literature then, there is a conclusive role for frontal brain regions in theory of mind. A point worth noting, however, involves the unclear localization with respect to laterality. This apparent hemispheric discrepancy in the research is thought to be due to the verbal and non-verbal nature of the tasks employed.

Lesion Studies

Lesion studies also support a role for frontal regions in ToM. Stone, Cohen and Knight (1998) investigated the effects of bilateral lesions to the orbito-frontal cortex and also unilateral (left) lesions to the dorsolateral frontal cortex. Participants performed a series of ToM tasks and the performance of patients with orbito-frontal lesions was similar to those with Asperger's Syndrome (a population with known ToM deficits), i.e. they displayed impairments in completion of ToM tasks (Stone et al., 1998). Stuss et al. (2001) tested patients with frontal lesions and non-frontal lesions and also found that lesions of the frontal lobe were associated with impaired ability to infer mental states of others.

Event-Related Potentials

Event-related brain potentials (ERPs) are an electrophysiological measure of neural activity during cognitive tasks. ERPs provide us with time-locked wave patterns elicited by neural electrical activity, which allows the tracing of the sequence of cognitive processes involved in a task (Rugg and Coles, 1995). ERP components are named by the direction of their deflection (i.e. positive or negative) and by the time window in which they appear. For example, "N140" describes a negative deflection occuring around 140ms. ERPs occurring in early time windows tend to be associated with the processing of the physical aspects of the stimulus. Later components are more often associated with the more complex, cognitive processes involved in the task (Rugg and Coles, 1995). Of the ERP components identified, some are thought to have potential significance in social cognition tasks. Here, the N400 and P300 have been selected as components expected to be elicited by the ToM/attribution of intention task employed.

<u>The N400</u>

The N400 component is characterized by a peak of negativity approximately 400 milliseconds (ms) after the onset of a stimulus. Its amplitude is sensitive to the abstract features of a stimulus, i.e. its meaning (Kutas and Federmeier, 2000; Rugg and Coles, 1995). Studies by Kutas and Hillyard (1980), which looked at sentences with semantically incongruent endings, were the first to describe the N400 component. Subjects were presented with short sentences, word by word, and if the final word was semantically incongruent a large N400 was observed. No appreciable N400 was elicited in response to sentences that ended in a predictable and semantically appropriate word. For example, "He spread the warm bread with socks," elicits a sizeable N400 component. Though the N400 was initially thought to be specific to linguistic stimuli, Barrett and Rugg (1989, 1990) have shown an N400 can be elicited and modulated with non-linguistic stimuli, for eg. pictures and faces. Altogether, the N400 is indicative of underlying semantic phenomena and many believe it is also a sign of contextual integration and integration of knowledge sources to form internal representations (Brown and Haggart, 1993; Kutas and Federmeir, 2000; West and Holcomb, 2002).

In their review of this component and schizophrenia, Kumar and Debruille (2004) highlight the idea that some language deficits displayed by subsets of the schizophrenic population (specifically patients with thought disorder) may be mediated by abnormal patterns of activation in semantic networks and subsequently reflected as an abnormal N400. Indeed, some investigations of patients with thought disorder reveal reduced N400 amplitude in response to semantic priming tasks, while others report the reverse (Andrews, et al., 1993). Despite this disparity, there is agreement that the problem lies with the integration of information as opposed to information processing (Andrews et al., 1993; Nestor et al., 1997; Kumar and Debruille, 2004).

The P300

The P300 or P3 is distinguished by a positive deflection which peaks around 300 ms (Donchin & Coles, 1988, Rugg & Coles, 1995) and is most commonly elicited in the auditory oddball paradigm (Jeon and Polich, 2001). The classical oddball paradigm consists of a series of two stimuli (for example, two tones of differing pitch) one of which occurs less often and the subject's task is to respond to the presentation of the rarer stimulus. The elicited waveform is maximal anywhere from 300-1200 ms (Rugg and Coles, 1995). The disparity in latency is a function of the complexity of the task; i.e. the more complex the task, the longer the latency of the positive component (Ruchkin, Johnson, Canoune, Ritter and Hammer, 1990). This dependent manipulation on the P300 has developed various theories relating the P300 to context and information assessment as well as stimulus evaluation (Rugg and Coles, 1995).

The P3b is a component of the P300 family that is maximal on posterior (Cz/Pz) sites. For complex stimuli like words, faces and objects, the P3b peaks at approximately 600ms; subsequently, this component is commonly referred to as the P600. Currently, the P3b is generally accepted as an index of the completion of processing (Sfagos et al., 2003). Some researchers assert its latency is a function of onset and duration of the

parsing processes while the amplitude is considered to reflect the cost of reprocessing (Garcia-Larrea and Cezanne-Bert, 1998). In this study, it is reasonable to expect the involved cognitive task to influence this later positive componnent. In fact, it is expected that the variations in the elicited P3b will reflect the up-dating of working memory as to the social knowledge that is relevant to the task at hand during a theory of mind task.

P3b and Schizophrenia

In general, literature reports diminished ERPs for patients with schizophrenia (Javitt et al., 1995; Boutros et al., 1997). Ford et al.'s (1994) review of the P300 component and schizophrenia highlights P3b amplitude reductions in schizophrenic patients. In response to an auditory selective attention task, patients with schizophrenia displayed smaller P3b amplitude compared to age- and sex-matched normal controls (Michie, Fox, Ward, Catts and McConaghy, 1990). McCarley et al. (1993) also report diminished P3b amplitudes on left temporal sites in schizophrenic patients in response to the auditory oddball task. Interestingly, they revealed significant reduction of gray matter in this region (superior temporal gyrus) as well. In the auditory oddball task, Higashima et al. (1998) measured P300 amplitude in patients who met DSM-III-R criteria for schizophrenia or schizophreniform disorder. Patients' symptoms were rated with the Positve and Negative Symptom Scale, and of the five symptom categories only thought disorder correlated with ERP amplitude. Specifically, subjects with the highest thought disorder ratings had the most reduced P3b amplitude.

Objectives and Hypotheses

Behavioural Predictions

This study will investigate associations between theory of mind and thought disorder at both the behavioural and the electrophysiological level. Patients will have their psychotic symptoms rated and will subsequently complete a task requiring the interpretation of the intention of others. If theory of mind ability is associated with thought disorder, we would expect patients with high ratings on thought disorder measures to have deficient ToM abilities and perform poorly on this task. Schizophrenic patients are expected to be less accurate in the intention-attribution task as compared to the normal subjects.

Electrophysiological Predictions

Event-related potentials will be recorded during the task. It is expected that the task will elicit noticeable wave patterns in the N400 and P300 time windows. The attribution of intention task asks subjects to infer intentions based on the facial expressions in the stimuli. This process necessarily requires a retrieval of internal knowledge and representations from past experiences. It is expected that the integration of these representations with those of the context of the task will be indexed by a prominent N400 deflection. The actual completion of the attribution process is reminiscent of the components that modulate P3b wave components. Divergent ERP wave patterns in patients with high ratings of thought disorder – as compared to those with less thought disorder and normal control subjects – are expected. In accordance with the literature, it is expected that ERP amplitudes will be diminished in patients with

more disorganization characteristics. Thus, normal control subjects are expected to have the largest ERPs, followed by those of patients with low ratings on thought disorder measures and then of those with profuse thought disorder.

As theory of mind is undoubtedly a higher order cognitive ability, we necessarily expect the emergent ERPs to be of greatest magnitude in frontal areas as compared to ERPs elicited from posterior sites. Prior studies highlight frontal activation, though the laterality of this activation is ambiguous. It is expected, however, that the non-verbal nature of our task will elicit higher magnitude ERPs from right-hemisphere electrodes (F3, Fc3) over electrodes in the left-hemisphere (F4, Fc4).

Methods

Subjects

A total of 30 patients meeting DSM-IV criteria for schizophrenia were tested. The patients were recruited from the Douglas Hospital and the LaSalle and Verdun outpatient clinics in Montreal, Quebec. One of the thirty patients was not taking medication at the time of the study (Chlorpromazine equivalents for all other patients are provided in Table 1). Twenty-six participants with no history of or current mental illness were recruited from newspaper advertisements to be used as normal control subjects. These control subjects were matched (in order) for gender, handedness, age and most recent level of education obtained. All subjects were fluent in either French or English, or bilingual. All participants gave informed consent to participate in the study, which was approved by the Douglas Hospital Research Ethics Board. Subjects received 10\$ per hour for their participation.

<u>Stimuli</u>

The face stimuli were pictures were taken from the MedBank. This bank includes the faces of 600 different people who have been photographed in standardized conditions. The photographs are color, front views of people whose faces do not depict full-blown expressions of emotions, rather subtle every-day life expressions for which there is vague consensus. Each face has been rated as looking positively-, negatively-, ambiguously-, or neutrally-intentioned by at least 50 naive people in a previous study (Debruille and Brodeur, 2001). A subset of 140 faces was selected for this experiment by choosing the faces that were rated positively-, negatively- or neutrally-intentioned, respectively, by the greatest percentage of people. Accuracy here should be considered as a general concept as the faces presented contained subtle expressions and subjects were asked to respond based on their first instinct. Forty of the faces were positively-intentioned, 40 negativelyintentioned and 60 neutral.

Procedure

Interviews

Patients' symptoms were assessed with the 24 item Brief Psychiatric Rating Scale (BPRS). This measure allows a well-validated rating of the various symptoms of schizophrenia and provides a good measure of thought disorder. Inclusion of ratings of other symptoms provides data for possible covariates in this study as well. Interviews were conducted in the patients' mother tongue (either French or English) by one of two researchers in the laboratory. The first interviewer (DS), a PhD student in clinical

psychology, was trained by a qualified BPRS trainer (SK) to high level of inter-rater reliability (better than 80%) on both videotaped and live interviews before the start of data collection. The second interviewer (NK), a MSc student in neuroscience, was trained by GS through video tapes, as well as through live interviews with a psychiatrist (JBD) and with DS until they reached an inter-rater reliability better than 80%.

Intention Attribution Task

Subjects were seated in a dimly lit, sound attenuated room and instructed to keep their gaze on a computer screen 0.8 m away from their eyes. The stimuli subtended a visual angle of about 5-. Each face was presented in the centre of the screen for 1000 ms. A "blink" command appeared for 400ms between 1800 and 2400 ms after the offset of the stimulus. Each trial lasted 4000ms. Subjects were required to judge the faces presented in one of three ways: neutrally-, positively-, or negatively-intentioned. Subjects gave their responses by pressing as quickly and as accurately as possible on an arrow key of a computer keyboard. The left arrow key was used for positive, the right for negative and the middle (down arrow) for neutral.

ERP Recording

EEGs were recorded from 28 electrodes placed according to the modified expanded 10-20 system and mounted in an elastic cap from ElectroCap International. Midline recording sites (Fz, FCz, Cz, Pz) were used, along with lateral electrode pairs over para-sagital sites (Fp1, Fp2, F3, F4, FC3, FC4, C3, C4, CP3, CP4, P5, P6, F7, F8, Ft7, Ft8, T3, T4, Tp7, Tp8, T5, T6, O2, O1). They were referenced to the left earlobe. FPz were used as a ground. Impedance of all electrodes was maintained below 5 K_. Vertical eye movements were detected by identifying large (i.e., greater than 75 microvolt) potentials having an identical timing and an opposite polarity at prefrontal (FP1 and FP2) electrodes relative to two electrodes placed below each eye. Horizontal movements were detected by identifying similar potentials on electrodes that were the closest to the outer canthi, namely, F7 and F8. EEGs were amplified 20 000 times by Contact Precision amplifiers with high and low frequency filters' half-amplitude cut-off set at 0.01Hz and 100Hz, respectively, with an additional 60Hz filter. The EEG signals were digitized at a rate of 256Hz and stored for offline analysis along with codes identifying the stimulus categories and subject's responses.

Off-line averaging was performed after manually rejecting trials artifacted by excessive EOG, myogram, amplifier saturations and/or analog to digital clipping. ERP baselines were computed from 200 ms before the onset of the stimulus. The ERP epoch includes data from 200 ms pre-stimulus to 800 ms post-stimulus presentation. ERP peaks were identified by visual inspection between 350 and 500 ms and from 500-800 ms post stimulus onset.

Data Analysis

Performance accuracy on the attribution of intention task was assessed with a oneway analysis of variance (ANOVA), with thought-disorder rating as the between subjects factor. Accuracy values were determined by the combination of two variables: correct and incorrect responses (i.e. % accuracy = number of correct responses/(number of correct responses + total number of incorrect responses)). Accuracy ratings, however should be regarded with a modicum of caution as the face stimuli contained subtle expressions and subjects were instructed to respond based on their own personal opinion.

A composite of errors committed in each intention category was created by summing the component errors. For example, adding the responses for negative and neutral for faces categorized as positive. These errors were analyzed with a one-way ANOVA.

Average reaction times were computed for each subject group during this task (i.e. the overall average of response time for all responses given). In addition, reaction times were created for correct and incorrect (average of the two incorrect response choices). These data were also analyzed with an ANOVA.

Frontal electrodes selected for analysis were F3/F4 and FC3/FC4. Prefrontal electrodes were omitted from analysis as visual inspection of ERPs on these sites depicted heavy residual blink artifact. Centro-parietal (CP3/CP4) and parietal (P3/P4) electrodes were analyzed to provide a control comparison for ERPs elicited on frontal sites. As ERPs are traditionally maximal on midline sites an analysis was performed on ERPs of electrodes on the midline. Event-related potential data was analyzed with a two-way analysis of variance (ANOVA). Level of thought disorder (high, low or none) was the between subjects factor and the within subjects factors were electrode and laterality. Post hoc analyses on specific means were conducted using Tukey's Honestly Significant Difference (HSD) tests for groups with unequal n's. Differences between means were considered significant when P<0.05. Statistical analyses were performed with the STATISTICA statistical program.

Results

Schizophrenic patients were categorized as having either high or low thought disorder based on the rating obtained for measure 15, Disorganized Speech, on the BPRS. Scores for all subjects with schizophrenia were ranked and separated with a median split. This method allows for different subjects in each group to assist in the visualization of the true ERP differences. The low and high thought disorder groups had means of 1.07 and 2.80, respectively. A t-test analysis proves the difference in BPRS rating between these two groups to be significant, P<0.001. Scores were compiled for the high and low thought disorder groups on measures of hallucination, delusion, disorganization and negative symptoms as these measures are known to be potential covariates with thought disorder. A significant difference was obtained between the groups for negative symptoms and this measure was entered as a covariate in the subsequent ANOVA to assess whether it was responsible for the differences observed. Results remained significant. All demographic data is presented in Table 1.

Behavioural Data

Mean response accuracy for the normal control, low and high thought disorder groups were, 69.82%, 63.08% and 57.60%, respectively. The ANOVA exposed a significant main effect for thought disorder, F(2, 53)=6.38, P=0.0033. A Tukey's HSD test for unequal N's revealed a significant difference between performance of the normal control participants and the patients with high thought disorder, P=0.0084.

An analysis of the errors made with respect to each intention category (positive, negative and neutral) revealed significant main effects for group (i.e. thought disorder

rating) F(2, 53)=6.38, P=0.0033 and for intention, F(2, 106)=37.0, P<0.00. Collapsing across the group effect, the mean errors for the positive, negative and neutral category are 18.69, 53.66 and 37.14 respectively. Post-hoc analysis (Tukey's HSD for unequal N's) of the intention effect revealed subjects made significantly more errors judging negative faces compared to those made for positive faces, P=0.0001; more errors for negative faces compared to neutral faces, P=0.0003; and more errors for neutral faces compared to positive faces, P=0.0003; and more errors for neutral faces compared to positive faces, P=0.0001; more errors for neutral faces compared to positive faces, P=0.0001; more errors for neutral faces compared to positive faces, P=0.0001; more errors for neutral faces compared to positive faces, P=0.0003; and more errors for neutral faces compared to positive faces, P=0.0001.

Analysis of overall reaction times in this experiment did not reveal any significant differences, F(2,53)=1.1, P=0.33, between normal controls, low or high thought disorder patients; means: 1030.09, 985.926 and 1130.18, respectively. Analysis of reaction times when divided into correct and incorrect responses exposes a main effect for reaction times which approaches significance, F(1, 53) = 3.81, P=0.056. Post-hoc analysis shows reaction times for correct responses (mean = 1026.23) were faster than those for incorrect responses (mean = 1065.72), P=0.049. The main effect of thought disorder on this measure was not significant, F(2, 53)=1.07, P=0.35.

Event-Related Potential Data

Frontal N400

In a two-way ANOVA for repeated measures with group (thought disorder rating) as the between subjects variable and electrode and laterality as the repeated within subjects factors, no significant main effect was observed for group, F(2, 53)=0.465, P=0.631. A significant main effect of laterality was observed, F(1, 53)=9.15, P=0.0038. A significant two-way interaction (electrode by laterality) was also observed, F(1,

53)=22.21, P<0.001. Decomposition of this interaction reveals ERPs obtained from lefthemisphere electrodes are larger in magnitude (mean = 1.738) than those from the righthemisphere (mean = 1.083), P=0.003. In addition, there was a trend for fronto-central electrodes (mean = 1.58) to have higher amplitudes than frontal electrodes (1.24), P=0.066. ERPs from all sites are represented in Figure 1.

Frontal P600

As previously mentioned, the term P3b refers to positive deflections, 300-1200 ms post stimulus onset, elicited traditionally by the auditory oddball paradigm. Here, however, we refrain from using "P3b" to refer to these components as our task is of a completely different nature. Instead, we will use "P600" to refer to our elicited waveforms.

Emergent waves in the P600 time window did not differ significantly with respect to group, F(2, 53)=0.728, P=0.487. The data, however, did display a significant main effect for laterality, F(1, 53)=18.08, P<0.001. A significant electrode by laterality interaction was observed as well, F(1, 53)=19.81, P<0.001. Left-hemisphere electrodes proved to impart larger amplitude ERPs (mean = 3.98mV) than right-hemisphere electrodes (mean = 2.96mV), P=0.0002).

Posterior N400

Analysis of ERPs in the N400 time window on equivalent parietal electrodes reveal significant main effects for electrode, F(1, 53)=63.97, P<0.001, and laterality, F(1, 53)=22.48, P<0.001. Post-hoc analysis shows posterior parietal electrodes to have larger amplitude ERPS (4.52mV) than centro-parietal electrodes (mean = 3.15mV), P=0.001. Here also, electrodes on the left side of the brain display larger amplitude ERPs (mean = 4.38mV) than right-side electrodes (mean = 3.29mV), P=0.0001. As expected there was no significant difference between groups, F(2, 53)=0.964, P=0.388.

Posterior P600

Significant main effects for electrode (F(1, 53)=12.18, P0.001) and laterality (F(1, 53)=13.24, P<0.001) were detected in this analysis. Similar patterns were observed for the P600 time window with respect to laterality, i.e. left side electrodes produce higher amplitude ERPs (mean = 5.722) than the right (mean = 4.720mV), P=0.0005. As well, posterior parietal brain areas emitted larger ERP amplitudes (mean = 5.574) than centroparietal areas (mean = 4.869), P=0.0008.

Midline N400

While no significant N400 effect was observed across the group variable (F(2, 53)=0.856, P=0.431), a significant main effect for electrode (F(3, 159)=30.77, P= P<0.001) was observed. Mean amplitudes for ERPs emergent in the N400 time window on Fz, FCz, Cz and Pz were 1.58, 1.41, 2.38 and 4.64mV, respectively. Emergent waveforms on Pz were larger than those on Fz (P<0.001), FCz (P<0.001) and Cz (P<0.001). The N400 obtained from Cz was also larger than that obtained from FCz (P=0.0415).

Midline P600

A significant main effect for electrode was observed in this analysis, F(3, 159)=17.71, P<0.001. No main effect for group was observed, F(2, 53)=1.73, P=0.188. However, a significant two-way group by electrode interaction was revealed, F(6, 159)=2.62, P=0.019. Independent analysis on the ERP waves emergent on PZ reveal patients with high levels of thought disorder (mean = 8.38mV) have larger P600 amplitudes than those with low thought disorder ratings (mean = 3.82mV), P=0.00652). The amplitude of P600 waves for normal subjects is 6.36mV and does not differ significantly from the low thought disorder group (P=0.184) or the high group (P=0.340).

Discussion

Performance on the attribution of intention task varied with the severity of thought disorder. Subjects who had high ratings of thought disorder performed worse than those with low thought disorder and significantly worse than normal control subjects. This finding corroborates those reported in literature, which highlight ToM impairments in patients with predominant disorganization characteristics (Greig et al., 2004; Hardy-Bayle, Sarfati and Passerieux, 2003; Sarfati and Hardy-Bayle, 1999; Safarti et al., 1999). The amplitude of emergent wave patterns in the N400 and P600 time window on frontal electrodes (F3/F4, FC3/FC4) did not vary with severity of thought disorder. These results are unexpected as ToM tasks are associated with frontal brain areas and as such we predicted significant, emergent phenomenon here. A bilateral division of wave amplitudes was seen across the entire brain; ERPs from the left hemisphere were consistently larger in amplitude than right-hemisphere wave patterns. These findings are similar to the localization reported in some studies (Fletcher et al.,

1995; Russell et al., 2000). However, given that differences in frontal activation were not replicated, and the left-hemisphere/ToM association has been elicited in verbal tasks, it is inappropriate to claim replication with other ToM tasks. While Frith's (1992) theory provided the impetus for the present investigation of thought disorder and ToM, neither confirming nor refuting evidence should be claimed as the behavioural task in this study may not have been appropriately matched.

No significant N400 or P600 was observed on Fz. While these findings are not in accordance with our predictions there are a number of likely explanations; one such lies in the nature of the task employed. While it is not far-fetched to assume the intention attribution task targets theory of mind ability, it has not been proven or correlated with any other classical ToM tasks. Though there is no, one globally accepted ToM task (Corrigan and Penn, 2001), a corroborating ToM task would bolster claims about the patients ToM abilities. It should be noted that attempts were made to substantiate the present intention attribution task. A non-verbal task was sought out to match the non-verbal character of our task. Safarti et al.'s (1999) task was acquired, however, it was not rigorous enough for all of the subjects (i.e. ceiling performance occurred for the normal controls). Also, the majority of the patients had been previously tested and relocating these people to administer Sarfati's test proved to be logistically impractical.

Assuming the intention attribution task is an adequate test of ToM ability, the results obtained may not be wholly interpretable due to problematic criteria used in the design of the task. Debruille and Brodeur (2001) cite the selection criteria for stimuli for the intention attribution task employed in this study. Photographs of faces categorized by the experimenters (as positively-, negatively-, or neutrally-intentioned) were randomly

presented to 50 individuals who were asked to judge the faces on these dimensions. Of the 60 positive faces, 78.4% judged them as such. For the negative and neutral faces, the percentages were 55.3 and 57.4, respectively. For the present intention attribution task, 40 of these photographs were selected from both the negative and positive categories; all 60 of the neutral faces were used. While the positive faces were agreed upon by a respectable majority, the inclusion of the negative and neutral faces is problematic. The behavioural data clearly shows significantly poorer performance in attributing intention to these faces; thus it is not unreasonable to question whether the quality of the emergent ERPs may have been tainted by the ambiguity of the negative and neutral faces. Balanced agreement across stimulus categories will increase the validity of the task and allow for interpretable and reliable results. Also, the N400 and P600 are classically maximal on posterior (centro-parietal and parietal, respectively) electrodes. With larger group sizes, it may be possible to tease out a robust frontal effect.

Analysis of posterior electrodes as a control ran as planned. There were no significant differences in ERP amplitudes corresponding to severity of thought disorder. Analysis of midline electrodes, however, revealed an unanticipated result; significant P600 amplitudes were discovered on Pz. Further analysis revealed greater P600 amplitude for patients with high ratings of thought disorder as compared to the low thought disorder group.

As previously mentioned, the P3b is generally accepted as an index of the completion of the processing of the stimulus (Sfagos et al., 2003). Specifically, the P3b is thought to reflect the completion of a coordinated process occurring after the detection of a target. Over the past three decades, reduced P3b amplitude in auditory paradigms in

patients with schizophrenia has been among the most robust and well-replicated effects in ERP research. Thus, it is surprising that the P600 amplitude elicited in this study is greater for symptomatic patients. Previous studies, however, employed classical oddball paradigms, necessarily different from the intention attribution task used in this study. While the P600 elicited here can be argued to be part of the P3b family (Gunter, Stowe and Mulder, 1997), it is likely that it reflects processing of a type of information somewhat different than that obtained in the auditory oddball task. Here, the P600 reflects the completion of processing of the intention of presented faces; stimuli certainly more complex than the auditory ones employed in the classical oddball.

One paper, however, presents findings similar to those of the present study. Andrews et al. (1993) reported a positive correlation between thought disorder rating and P600 amplitude. Also, patients with obsessive-compulsive disorder patients are reported to have larger P600 amplitudes which is thought to be due to increased attention to abnormal features (Papageoriou and Rabavilas, 2003). It is not inconceivable to apply a similar explanation to the patients in this experiment. Patients with thought disorder have difficulties inhibiting interfering thoughts and ideas to focus on the task/conversation at hand (Barlow and Durand, 1998); this idea is reminiscent of the excessive spreading of activation in semantic networks noted by Kumar and Debruille (2004). In the present study, this group of patients may have expressed their impairment through an overactivation of representations elicited by the stimuli. While reaction time data shows no difference in the amount of time each group of subjects took to respond, the differential ERP pattern implies a very different processing approach. It is possible that the more

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thought-disordered patients gleaned an excessive amount of information from each stimulus to create an impression of the intention portrayed.

If the results from this study are to be taken as a reflection of electrophysiological underpinnings of ToM processing, the significant posterior activation requires an explanation. Theory of mind is a higher-order cognitive function and inevitably requires prefrontal areas, but this fact does not preclude the involvement of posterior areas in certain aspects of ToM processing. One posterior brain region worth investigating is the superior temporal sulcus (STS). Literature reports findings which can be interpreted to elucidate important elements of the mentalizing process. Non-human primates viewing movement of intentional actions display significant increases in activation in cell populations in the STS (Jellema, Baker, Wicker and Perrett, 2000). Also, human research reports activation of the STS in tasks requiring the perception of direct and averted eye gaze (Wicker, Michel, Henaff and Decety, 1998; Puce, Allison, Bentin, Gore and McCarthy, 1998; Calder et al., 2002). Calder et al. (2002) highlight the important point that, in addition to signaling the object of someone's attention, the gaze of the eye can also reflect that persons' intention concerning the object; undoubtedly an integral part of the ToM process. As such, these stated findings point to a definitive role for the STS in the sub-systems involved in ToM competence.

Indeed, when tasks specifically geared to target ToM abilities are employed, researchers report activation of the posterior STS. An early study investigating brain areas involved in understanding theory of mind stories highlighted activation in the right posterior STS (Fletcher et al., 1995). Goel, Grafman, Sadato and Hallett (1995) assess ToM processes by asking subjects to infer another's thoughts of the functions of random

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objects. PET scans during this task revealed increased cerebral blood flow in the STS. Sarfati's cartoon task also elicits activation of the STS during PET scans (Brunet et al., 2000). Gallagher et al. (2000) replicated the finding of increased posterior activation in an fMRI study requiring comprehension of ToM stories. Brunet, Sarfati, Hardy-Bayle and Decety (2003) developed a ToM task, which required subjects to create a representation of another person's intentions and posterior STS activation was displayed during this task. Blakemore et al. (2003) also report activation in posterior regions in tasks involving ToM-like abilities. Thus, an association exists between the process of mentalizing and posterior brain regions at the temporo-parietal junction.

In their review on brain regions associated with ToM, Frith and Frith (2003) allude to the idea that STS activation could reflect a memory retrieval process. In the present task, the process of attributing intention necessarily requires subjects to call on internal representations of the facial expressions they encounter. Sfagos et al. (2003) also suggest the P600 component may be related to working memory. One possible theory then, is that revision of working memory is a key component to the ToM process. Indeed, during our everyday encounters with other individuals we are constantly confirming, modifying or extinguishing our representations of others in our social world. A fine balance must be struck, however, as over- or under-activation can result in erroneous inferences and/or predictions about others; for example, the apparent over-activation in patients with high levels of thought disorder (Ford, 1994; Kumar and Debruille, 2004).

Frith and Frith (2003) also suggest STS activation as an index of knowledge of complex behaviour. The process of attributing intention to another person, which

requires an assessment of their emotional expression, mental state and incorporation of this knowledge is, in essence, complex. As such, the posterior pattern of activation elicited in this study is consistent with their concept. The crucial criticism of this line of thought, however, is that the Pz generators are not traditionally thought to be in the STS. Nevertheless, the EEG reflects changes in electrical activity of large populations of neurons in the cerebral cortex and the location of the Pz electrode is just medial to posterior STS sites and it is not inconceivable that this area is contributing to emergent electrical activity on Pz.

Areas providing activation to sites at Cz are thought to signal the existence of response conflict or multiple response possibilities (Petit,1998; Botvinick, 1999). This idea fits with the concept of an over-activation or hyper-processing of stimuli as the major problem for patients with thought disorder. Perhaps those with high thought disorder are so disorganized that they are processing so much information and attributing so many intentions to the face that they are conflicted about their eventual response, while patients with low thought disorder make less of an effort because they are working with less stimulus information. This explanation might be critical in interpreting the ERP pattern from normal control subjects. Their P600 amplitude was between those of the high and low thought disorder groups; suggesting that normal processing of another's mental state lies somewhere between the hyperactive over-processing by highly disorganized patients and the relative apathy of patients without.

Nevertheless, research shows some schizophrenic patients are capable of changing their mental states. Patients were initially interviewed about their delusions and exhibited a lack of insight, but after being asked to change their perspective from first person to third person some of the subjects were able to gain insight (Gambini, Barbieri and Scarone, 2004). These findings point to the value of ToM research in schizophrenic patients and provide hope for the future of their social interactions.

Conclusion

Results from this study confirm impaired performance for schizophrenic patients on tasks requiring theory of mind ability. Results also highlight the P600 component of the P3b family as a potential correlate for theory of mind ability. The significant differences between groups directs attention to posterior brain sites, such as the STS, as potential mediators of ToM ability. Ideally, the abnormal P600/P3b deflections will eventually be used as predictors of a cognitive breakdown fundamental to schizophrenia. Further research with corroborating ToM tasks and larger samples will be necessary to solidify the association between the P600/P3b, attribution of intention to others and schizophrenia.

References

Abu-Akel, A. (2003). A neurobiological mapping of theory of mind. <u>Brain</u> <u>Research Reviews, 43,</u> 29-40.

Alain, C., Hargrave, R. and Woods. D.L. (1998). Processing of auditory stimuli during visual attention in patients with schizophrenia. <u>Biological Psychiatry, 44</u>,

1151–1159.

American Psychiatric Association. (2000). <u>The Diagnostic and statistical manual</u> of mental disorders <u>DSM-IV-TR (Text Revision)</u> (4th ed.). Washington, DC.: American Psychiatric Association.

Andrews, S., Shelley, A.M., Ward, P.B., Fox, A., Catts, S.V. and McConaghy, N. (1993). Event-related potential indices of semantic processing in schizophrenia.

Biological Psychiatry, 34, 443-58.

Barlow, D. and Durand, V.M. (1998). <u>Abnormal Psychology</u>. New York: Brooks/Cole Publishing Company.

Baron-Cohen, S. (1994). <u>Mindblindness: An essay on autism and theory of mind.</u> Massachusetts: The MIT Press.

Baron-Cohen, S., Ring, H., Moriarty, J., Schmitz, B., Costa, D. and Ell, P. (1994). Recognition of mental state terms. Clinical findings in children with autism and a functional neuroimaging study of normal adults. <u>British Journal of Psychiatry, 165,</u> 640-49.

Bartholow, B.D., Fabiani, M., Gratton, G., and Bettencourt, B.A. (2001). A Psychophysiological examination of cognitive processing of and affective responses to social expectancy violoations. <u>Psychological Science, 12,</u> 197-204. Blakemore, S.J., Boyer, P., Pachot-Clouard, M., Meltzoff, A., Segebarth, C. and Decety, J. (2003). The detection of contingency and animacy from simple animations in the human brain. <u>Cerebral Cortex, 13</u>, 837-844.

Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S. and Cohen, J.D. (1999). Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature, 402, 179-181.

Brunet, E., Sarfati, Y., Hardy-Bayle, M.C. and Decety J. (2000). A PET investigation of the attribution of intentions with a nonverbal task. <u>Neuroimage, 11, 157-</u>166.

Brunet, E., Sarfati, Y., Hardy-Bayle, M.C. and Decety J. (2003). Abnormalities of brain function during a nonverbal theory of mind task in schizophrenia. Neuropsychologia, 41, 1574-82.

Calarge, C., Andreasen, N.C. and O'Leary, D.S. (2003). Visualizing how one brain understands another: a PET study of theory of mind. <u>American Journal of</u> <u>Psychiatry, 160, 1954-64</u>.

Calder, A.J., Lawrence, A.D., Keane, J., Scott, S.K., Owen, A.M., Christoffels, I. and Young, A.W. (2002). Reading the mind from eye gaze. <u>Neuropsychologia, 40,</u> 1129-38.

Corcoran, R. (2000). Theory of mind in other clinical conditions: is a selective 'theory of mind' deficit exclusive to autism? In Baron-Cohen, S., Tager-Flusberg, H. and Cohen, D.J., (Eds.). <u>Understanding Other Minds: Perspectives From Developmental</u> <u>Cognitive Neuroscience.</u> Oxford: Oxford University Press. Corcoran, R. (2001). Theory of mind and schizophrenia. In Corrigan, P.W. and Penn, D.L., (Eds.). <u>Social Cognition and Schizophrenia.</u> Washington: American Psychological Association.

Corcoran, R., Cahill, C. and Frith, C.D. (1997). The appreciation of visual jokes in people with schizophrenia; a study of 'mentalizing' ability. <u>Schizophrenia Research</u>, <u>24</u>, 319-327.

Corcoran, R. and Frith, C.D. (2003). Autobiographical memory of theory of mind: Evidence of a relationship in schizophrenia. <u>Psychological Medicine</u>, 33, 897-905.

Corcoran, R., Mercer, G. and Frith, C.D. (1995). Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. <u>Schizophrenia Research, 17,</u> 5-13.

Corrigan, P.W. and Penn, D.L. (2001). <u>Social Cognition and Schizophrenia.</u> Washington: American Psychological Association.

Debruille, J.B. and Brodeur, M. (2001). Coding facial expressions: Idiosyncrasy

of automatic processes and sociality of contextual processes. Manuscript in preparation.

Dennet, D.C. (1978). Beliefs about beliefs. <u>Behavioral and Brain Sciences, 4</u>, 568-570.

Donchin, E. and Coles, M.G.H. (1988). Is the P300 component a manifestation of context updating? <u>Behavioral and Brain Sciences</u>, 11, 357-374.

Doody, G.A., Gotz, M., Johnstone, E.C., Frith, C.D. and Owens, D.G. (1998). Theory of mind and psychoses. <u>Psychological Medicine</u>, 28, 397-405. Drury, V.M., Robinson, E.J. and Birchwood, M. (1998). Theory of mind' skills during an acute episode of psychosis and following recovery. <u>Psychological Medicine</u>, <u>28</u>,1101-12.

Fletcher, P.C., Happe, F., Frith, U., Baker, S.C., Dolan, R.J., Frackowiak, R.S.J. and Frith, C.D. (1995). Other minds in the brain: A functional imaging study of "theory of mind" in story comprehension. <u>Cognition, 44</u>, 283-96.

Ford, J.M., White, P.M., Csernansky, J.G., Faustman, W.O., Roth, W.T. and Pfefferbaum, A. (1994). ERPs in schizophrenia: effects of antipsychotic medication. <u>Biological Psychiatry, 36,</u> 153-70.

Frith, C.D. (1992). <u>The Cognitive Neuropsychology of Schizophrenia</u>. Hillsdale: Lawrence Erlbaum Associates.

Frith, C.D. and Corcoran, R. (1996). Exploring 'theory of mind' in people with schizophrenia. <u>Psychological Medicine</u>, 26, 521-30.

Frith, U. and Frith. C.D. (2003). Development and neurophysiology of mentalizing. Philosophical Transactions Royal Society of London: Biological Sciences, 358, 459-473.

Gambini, O., Barbieri, V. and Scarone, S. (2004). Theory of Mind in schizophrenia: first person vs third person perspective. <u>Consciousness and Cognition, 13</u>, 39-46.

Garcia-Larrea L, Cezanne-Bert G. (1998). P3, positive slow wave and working memory load: a study on the functional correlates of slow wave activity. <u>Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section 108,</u> 260-273. Garety, P.A. and Freeman, D. (1999). Cognitive approaches to delusions: a critical review of theories and evidence. <u>British Journal of Clinical Psychology</u>, 38, 113-154.

Goel, V., Grafman, J., Sadato, N. and Hallett M. (1995). Modeling other minds. Neuroreport, 6,1741-6.

Gooding, D.C. and Tallent, K.A. (2004). Nonverbal working memory deficits in schizophrenia patients: Evidence of a supramodal executive processing deficit <u>Schizophrenia Research, 68,</u> 189-201.

Gordon, A.C. and Olson, D.R. (1998). The relation between acquisition of a theory of mind and the capacity to hold in mind. <u>Journal of Experimental and Child</u> <u>Psychology 68,</u> 70-83.

Green, M.F. (2001). <u>Schizophrenia revealed: from neurons to social interactions.</u> New York: W.W. Norton.

Greig, T.C., Bryson, G.J. and Bell, M.D. (2004). Theory of mind performance in schizophrenia: diagnostic, symptom, and neuropsychological correlates. Journal of <u>Nervous and Mental Disorders, 192</u>, 12-8.

Gunter, T.C., Stowe, L.A. and Mulder, G. (1997). When syntax meets semantics. Psychophysiology, 34, 660-676.

Happe, Francesca. (1994). An advanced test of theory of mind: Understanding of story characters' thoughts and feelings by able autistic, mentally handicapped and normal children and adults. Journal of Autism and Developmental Disorders, 24, 129-54.

Happe, Francesca. (1995). <u>Autism: an introduction to psychological theory.</u> Massachusetts: Harvard University Press. Happe, F., Ehlers, S., Fletcher, P., Frith, U., Johansson, M., Gillberg, C., Dolan, R., Frackowiak, R. and Frith, C. (1996). Theory of mind' in the brain. Evidence from a PET scan study of Asperger syndrome. <u>Neuroreport, 8</u>, 197-201.

Hardy-Bayle, M.C, Sarfati, Y. and Passerieux, C. (2003). The cognitive basis of disorganization symptomatology in schizophrenia and its clinical correlates: toward a pathogenetic approach to disorganization. <u>Schizophrenia Bulletin, 29,</u> 459-71.

Heavey, L., Phillips, W., Baron-Cohen, S. and Rutter, M. (2000). The awkward moments test: A naturalistic test of social understanding in autism. Journal of Autism and Developmental Disorders, 30, 225-36.

Heydebrand, G., Weiser, M., Rabinowitz, J., Hoff, A.L., DeLisi, L.E. and Csernansky, J.G. (2004). Correlates of cognitive deficits in first episode schizophrenia. <u>Schizophrenia Research, 68,</u> 1-9.

Higashima, M., Urata, K., Kawasaki, Y., Maeda, Y., Sakai, N., Mizukoshi, C., Nagasawa, T., Kamiya, T., Yamaguchi, N. and Koshino, Y. (1998). P300 and the thought disorder factor extracted by factor-analytic procedures in schizophrenia. <u>Biological</u> <u>Psychiatry</u>, 44, 115-20.

Hutton, S.B., Murphy, C., Joyce, E.M., Rogers, R.D., Cuthbert, I., Barnes, T.R., McKenna, P.J., Sahakian, B.J. and Robbins, T.W. (2002). Decision making deficits in patients with first-episode and chronic schizophrenia. <u>Schizophrenia Research</u>, 55, 249-57.

Jaeger, J., Czobor, P. and Berns, S.M. (2003). Basic neuropsychological dimensions in schizophrenia. <u>Schizophrenia Research</u>, 65, 105-16.

Jellema, T., Baker, C. I., Wicker, B. and Perrett, D. I. (2000). Neural

representation for the perception of the intentionality of actions. <u>Brain and Cognition 44</u>, 280–302.

Kumar, N. and Debruille, J.B. (2004). Semantics and N400: insights for schizophrenia. Journal of Psychiatry and Neuroscience, 29, 89-98.

Meisenzahl, E.M., Frodl, T., Muller, D., Schmitt, G., Gallinat, J., Zetzsche, T., Marcuse, A., Juckel, G., Leinsinger, G., Hahn, K., Moller, H.J. and Hegerl, U. (2004). Superior temporal gyrus and P300 in schizophrenia: a combined ERP/structural magnetic resonance imaging investigation. Journal of Psychiatric Research, 38, 153-62.

Michie, P.T., Fox, A.M., Ward, P.B., Catts, S.V. and McConaghy, N. (1990). Event-related potential indices of selective attention and cortical lateralization in schizophrenia. <u>Psychophysiology</u>, <u>27</u>, 209-27.

Langdon, R., Coltheart, M., Ward, P.B. and Catts, S.V. (2002). Disturbed communication in schizophrenia: the role of poor pragmatics and poor mind-reading. <u>Psychological Medicine</u>, 32, 1273-84.

McCarley, R.W., Shenton, M.E., O'Donnell, B.F., Faux, S.F., Kikinis, R., Nestor, P.G. and Jolesz, F.A. (1993). Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. <u>Archives of General Psychiatry, 50</u>, 190-7.

Michie, P.T., Fox, A.M., Ward, P.B., Catts, S.V. and McConaghy N. (1990). Event-related potential indices of selective attention and cortical lateralization in schizophrenia. <u>Psychophysiology</u>, 27, 209-27. Nestor, P.G., Kimble, M.O., O'Donnell, B.F., Smith, L., Niznikiewicz, M.,

Shenton, M.E. and McCarley, R.W. (1997). Aberrant semantic activation in

schizophrenia: a neurophysiological study. American Journal of Psychiatry, 154, 640-46.

Novak g., and Pelaez, M. (2004). <u>Child and adolescent development: A</u> behavioral and systems approach. Thousand Oaks: Sage Publications.

Papageorgiou, C.C. and Rabavilas, A.D. (2003). Abnormal P600 in obsessive-compulsive disorder. A comparison with healthy controls. <u>Psychiatry</u> Research, 119, 133-143.

Perner, J., Frith, U., Leslie, A.M. and Leekam, S.R. (1989). Exploration of the autistic child's theory of mind: Knowledge, belief and communication. <u>Child</u> <u>Development 60</u>, 689-700.

Pickup, G.J. and Frith, C.D. (2001). Theory of mind impairments in schizophrenia: symptomatology, severity and specificity. <u>Psychological Medicine, 31</u>, 207-20.

Pillmann, F., Bloink, R., Balzuweit, S., Haring, A. and Marneros, A. (2003).
Personality and social interactions in patients with acute brief psychoses. Journal of Nervous and Mental Disorders, 191, 503-8.

Premack, D. and Woodruff, G. (1978). Chimpanzee problem-solving: a test for comprehension. <u>Science</u>, 202, 532-535.

Puce, A., Allison, T., Bentin, S., Gore, J.C. and McCarthy, G. (1998). Temporal cortex activation in humans viewing eye and mouth movements. <u>Journal of Neuroscience</u>, 18, 218-99.

Rosenzweig, M.R., Leiman, A.L. and Breedlove, S.M. (1996). <u>Biological</u> <u>Psychology.</u> Sunderland: Sinauer Associates, Inc.

Ruchkin, D.S., Johnson, R. Jr., Canoune, H.L., Ritter, W. and Hammer, M. (1990). Multiple sources of P3b associated with different types of information.

Psychophysiology, 27, 157-76.

Rugg, M.D. and Coles, M.G.H. (1995). <u>Electrophysiolgy of Mind: Event-Related</u> Brain Potentials and Cognition. New York: Oxford University Press.

Russell, T.A., Rubia, K., Bullmore, E.T., Soni, W., Suckling, J., Brammer, M.J., Simmons, A., Williams, S.C. and Sharma, T. (2000). Exploring the social brain in schizophrenia: left prefrontal underactivation during mental state attribution.

American Journal of Psychiatry, 157, 2040-2042.

Sarfati, Y. and Hardy-Bayle, M.C. (1999). How do people with schizophrenia explain the behaviour of others? A study of theory of mind and its relationship to thought and speech disorganization in schizophrenia. <u>Psychological Medicine</u>, 29, 613-20.

Sarfati, Y., Hardy-Bayle, M.C., Brunet, E. and Widlocher, D. (1999). Investigating theory of mind in schizophrenia: influence of verbalization in disorganized and non-disorganized patients. <u>Schizophrenia Research</u>, <u>37</u>, 183-90.

Satterfield, J.H., Schell, A.M. and Nicholas, T. (1994). Preferential neural processing of attended stimuli in attention-deficit hyperactivity disorder and normal boys. <u>Psychophysiology</u>, 31, 1-10.

Sfagos, C., Papageorgiou, C.C., Kosma, K.K., Kodopadelis, E., Uzunoglu, N.K., Vassilopoulos, D. and Rabavilas A.D. (2003). Working memory deficits in multiple sclerosis: a controlled study with auditory P600 correlates. Journal of Neurology, Neurosurgery and Psychiatry, 74,1231-5.

Stone, V.E., Baron-Cohen, S. and Knight, R.T. (1998). Frontal lobe contributions to theory of mind. Journal of Cognitive Neuroscience, 10, 640-656.

Stuss, D.T., Gallup, G.G. Jr. and Alexander, M.P. (2001). The frontal lobes are necessary for 'theory of mind'. <u>Brain,124</u>, (Pt 2), 279-286.

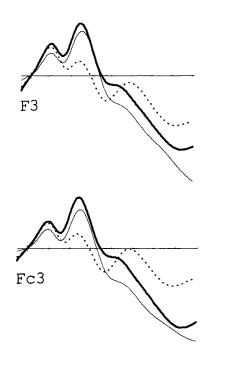
Wicker, B., Michel, F., Henaff, M.A. and Decety, J. (1998). Brain regions involved in the perception of gaze: a PET study. <u>Neuroimage</u>, 8, 221-27.

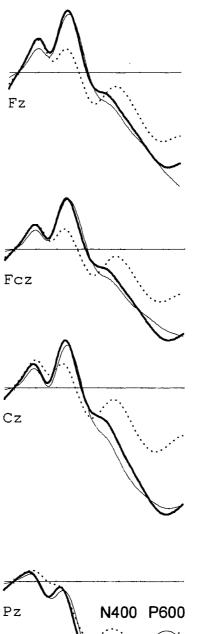
Wimmer H. and Perner, J. (1983). Beliefs about beliefs: Representation and constraining function of wrong beliefs in young children's understanding of deception. <u>Cognition 13</u>, 103–128.

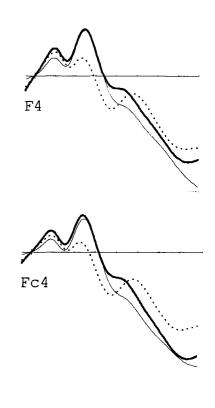
Zuckerman, M. (1999). <u>Vulnerability to Psychopathology: A Biosocial Model.</u> Washington: American Psychological Association.

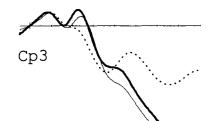
	High Thought Disorder (n=15)			Low Thought Disorder (n=15)		Normal Control (n=26)			
	mean	stddev	range	mean	stddev	range	mean	stddev	range
Demographic Data									
Age	27.53	7.06	19-42	29.67	8.36	19-45	27.96	7.18	18-43
Education (years)	11.93	2.94	9-19	10.38	1.94	8-14	11.23	1.27	9-14
Sex (M/F)	10/5			12/3			20/6		
Illness Duration (years)	6.21	4.76	1-16	5.18	4.62	1-18			
Clincal Data			······································						
BPRS Scores									
Total	52.13	7.17	31-66	43.60	10.11	38-62			
Thought Disorder	2.80	0.77	2-4	1.07	0.26	1-2			
Hallucination	3.13	2.50	1-8	3.13	2.29	1-7			
Delusion	2.87	1.92	1-6	3.07	1.53	1-6			
Disorganization	6.13	1.64	4-9	3.73	1.10	3-6			
Negative Symptoms	7.27	1.98	4-10	5.67	2.32	4-12			
Medication	······································						· · · · · · · · · · · · · · · · · · ·	- <u>-</u>	
Chlorpromazine									
equivalence (mg/day)	505.31	466.34	0-1575	426.07	354.09	100- 1267			

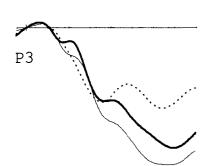
Figure 1

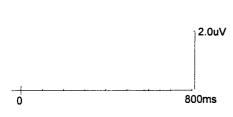


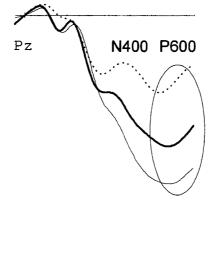


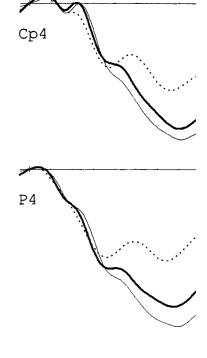












- High Thought Disorder Low Thought Disorder Normal Control