PERCEPTION OF BIOLOGICAL MOTION IN SCHIZOPHRENIA

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CHAPTER I

OVERVIEW

This dissertation aims to augment our understanding of visual perception deficits and their relationship with impaired social functioning in schizophrenia and obsessive-compulsive disorder (OCD). The central role of visual perception in all aspects of human behavior is undisputed. Rapid and accurate perception of the environment is necessary for survival as well as in facilitating effective social functioning. In this context, the perception of biological motion (Johansson, 1973), a specific type of visual information that carries rich social information, is a key area of research that should have important implications for understanding the role of perception in social behavior (Blake & Shiffrar, 2007).

Schizophrenia is a major mental disorder that is characterized by psychotic symptoms such as hallucinations, delusions and thought disorder, cognitive deficits, and impaired social functioning. Hallucinations are obviously abnormal perceptual experiences but other more subtle perceptual problems have long been considered to be at the core of this disorder. There is a general agreement that processing of rapid, dynamic visual information is impaired in schizophrenia (Butler & Javitt, 2006: review) and that visual perceptual deficits are associated with social impairments (Sergi & Green, 2002).

Social deficits in schizophrenia have been explored most extensively within the framework of the theory of mind (Baron-Cohen, 1995) and the putative neuronal network underlying 'social brain', which includes the orbitofrontal cortex (OFC), the superior

temporal cortex (STC), and the amygdala (Burns, 2006). Interestingly, past studies of biological motion perception in healthy adults have identified the STC as the specific region that is responsive to this type of motion signal (Grossman et al., 2000) and individuals with autism, a disorder of social deficit, have been shown to be impaired in biological motion perception (Blake et al, 2003).

Nevertheless, there have been no systematic attempts to investigate perception of biological motion in schizophrenia; which is the primary interest of this dissertation. Therefore, a series of experiments were conducted to investigate biological motion perception in schizophrenia and to find underlying neural mechanisms using both psychophysical and functional brain imaging methods. Finding new deficits in schizophrenia is relatively easy and therefore it is important to ask to what extent a deficit in biological motion perception leads to new insight into schizophrenia rather than reflects a general deficit that is common to all mental disorders. While OCD is very different from schizophrenia, it also shares some common characteristics in terms of impaired social functioning and thus may offer a useful contrast. Furthermore, some OCD patients with schizotypal personality show similar cognitive deficits as schizophrenia patients (Shin et al., 2008).

In CHAPTER II, previous studies on visual perception deficits, impaired social functioning in schizophrenia, and biological motion perception in healthy people will be reviewed. In addition, the goals and hypotheses will be outlined. CHAPTER III will focus on a series of behavioral experiments of biological motion perception in schizophrenic patients and healthy individuals. In CHAPTER IV, the neural mechanisms underlying perception of biological motion in schizophrenic and healthy subjects will be

explored through a functional magnetic resonance imaging (fMRI) study. CHAPTER V will describe a study of visual perception including biological motion perception in patients with OCD. Finally, I will discuss the implications emerging from the behavioral and imaging results in CHAPTER VI.

CHAPTER II

VISUAL DEFICITS, SOCIAL FUNCTIONING AND PERCEPTION OF BIOLOGICAL MOTION IN SCHIZOPHRENIA

Schizophrenia

Schizophrenia is a complex and severe mental disorder that affects about 1% of the population. It has been clinically characterized by positive symptoms such as hallucinations and delusions, negative symptoms such as flat affect and social withdrawal, and disorganized symptoms including thought disorder and motor disturbance (American Psychiatric Association, 1994). Although it already has been suggested that a combination of genetic and environmental factors might lead to the onset of schizophrenia (Lewis & Levitt, 2002), the biological aspects of the illness are yet to be determined. The recent advances in cognitive neuroscience, genetics, psychopharmacology, and brain imaging techniques have contributed the understanding of possible causes and have led to improvements in the functional outcome of schizophrenia.

In addition to the clinical aspects of schizophrenia, the importance of cognitive deficits such as attentional problems (Nuecheterlein, 1991), impaired working memory (Park & Holzman, 1992; 1993), and abnormal executive functioning (Haut et al., 1996) have become increasingly evident. This wide range of cognitive deficits is thought to be better at predicting the prognosis of schizophrenia patients than traditional clinical symptoms (Green, 1996; Liddle, 2000; Meltzer, Thompson, Lee, & Ranjan, 1996). Moreover, all of these deficits have implicated inefficient functioning of the prefrontal

cortex (PFC)(Carter et al., 1998; Goldman-Rakic, 1994; Manoach et al., 2000). However, altered brain functions of schizophrenia patients are not restricted to the PFC. This is not surprising if we consider a variety of clinical symptoms and neurocognitive abnormalities. Indeed, neural dysfunction in schizophrenia extends to perception-related areas, including the temporal cortex (Shenton et al., 1992), visual cortex (Selomon, Rajkowska, & Goldman-Rakic, 1995) and the thalamus (Andreason, 1997), suggesting deficits of perceptual nature. There is evidence suggesting that impaired perceptual processing may interact with or mediate deficits in cognitive functions (e.g. Haenschel et al., 2007; Hartmen, Steketee, Silva, Lanning, & McCann, 2002; Tek et al., 2002). Furthermore, growing body of literature has consistently reported specific visual perceptual abnormalities (e.g. Butler et al., 2001; Chen et al., 1999a; Chen, Levy, Nakayama, & Matthysse, 1999b; Green, Nuechterlein, & Mintz, 1994a,b).

Another line of studies have focused on patients' social functioning, and it has been well established that schizophrenia patients exhibit severe and enduring social deficits. For example, patients exhibit impaired theory of mind (ToM), which refers to ability to infer the actions and intentions of other people (Baron-Cohen, 1995). Social deficits can be parsed into perceptual and cognitive components. While cognitive deficits in relation to social functioning have been extensively investigated in studies on schizophrenia, there has been little attempt to relate visual perception to social functioning. Visual perception can eventually affect one's behavioral and social outcome, and some visual motion cues can carry rich social information (e.g. "biological motion"). Therefore, this dissertation aims to investigate how schizophrenia patients process socially-relevant visual stimuli.

In the next sections, visual deficits and impaired social functioning in schizophrenia, as well as, past studies on biological motion perception are briefly reviewed.

Visual deficits in schizophrenia

Patients with schizophrenia experience subjectively distorted perceptual world (e.g. consider hallucinations). Indeed, clinical studies using a structured interview questionnaire indicated that a large proportion of schizophrenia patients experience distorted perception of motion, color, depth, size, and facial expression (e.g. Bunney et al., 1999; Cutting & Dunne, 1986).

Deficits in early visual processing before motion perception

Perceptual deficits revealed by empirical studies in schizophrenia also have been particularly well documented in the visual system. It is worthwhile to note that those psychophysical and physiological studies have yielded converging evidence suggesting impairment of the magnocellular visual processing stream (or transient visual channels) that is mainly involved in processing low spatial, and high temporal frequencies and dynamic visual stimuli. On the other hand, the parvocellular (sustained) visual processing stream that is responsible for processing high spatial, low temporal frequencies and color, shape information is relatively intact in schizophrenia (Butler & Javitt, 2005). For example, patients with schizophrenia exhibit significantly longer-lasting visual backward masking (VBM) effect compared to healthy people (Braff et al., 1991; Butler, Harkavy-Friedman, Amador, & Gorman, 1996; Butler et al., 2001; 2002; Green et al., 1994a,b; Green & Nuechterlein, 1999; Rund, 1993; Saccuzzo & Braff, 1981; Schechter, Butler,

Silipo, Zemon, & Javitt, 2003). VBM refers to a phenomenon in which the visibility of a briefly presented target is reduced by a mask presented very shortly after the target. The VBM effect is thought to occur because the transient visual activity evoked by the mask interrupts the sustained visual channel activity of the target, or the sustained activities to both mask and target are integrated (Breitmeyer & Ganz, 1976). Past results suggested that the interruption mediated by transient visual activities is abnormal in schizophrenia at the visual processing stage around the primary visual cortex (V1) (Green et al., 1994a,b). Although the idea of a compromised transient visual channel in the early visual processing mainly comes from VBM studies, other studies have also revealed that patients show consistent deficits if a visual task taps into the functioning of the transient visual channels. For example, patients with schizophrenia have difficulty in discriminating contrast of two sinusoidal gratings that have low to medium contrast regardless of whether the two grating are presented simultaneously (O'Donnell et al., 2002) or one after the other (Keri, Antal, Szekeres, Benedek, & Janka, 2002).

Physiological studies also provide converging evidence: studies using the visual evoked potential (VEP) recordings consistently found that the amplitude of VEP component P1, which mainly reflects activities of the transient magnocellular visual pathways, is significantly reduced in schizophrenia (Butler et al., 2001; Butler & Javitt, 2005; Foxe, Doniger, & Javitt, 2001; Schechter et al., 2003). These abnormally reduced transient activities are observed in broad scalp sites including extrastriate dorsal areas. This reduction suggests that schizophrenia patients are also impaired in perceiving more complex visual stimuli (Cadenhead, Serper, & Braff, 1998). Indeed, another prominent visual deficit observed in schizophrenia is impaired motion perception (Chen et al.,

1999a,b; Chen, Nakayama, Levy, Matthysse, & Holzman, 2003b; Chen, Levy, Sheremata, & Holzman, 2004; Chen, Bidwell, & Holzman, 2005; Li, 2002; Schwartz, Maron, Evans, & Winstead, 1999; Stuve et al., 1997).

Deficits in motion perception

Impaired motion perception is another well-documented abnormality of visual processing in schizophrenia. Motion perception deficits can be considered particularly important in terms of their effect on behavioral and social outcome: movement of an object within the visual field carries rich perceptual information about the three dimensional properties of the object and their relative positions (Sekuler, Watamaniuk, & Blake, 2002). Psychophysical studies on general motion perception in schizophrenia have indicated that the deficits manifest in a selective and specific manner (Chen et al., 1999a; 2003b; Li, 2002; O'Donnell et al., 1996; Tadin et al., 2006). For example, a psychophysical study by Chen and colleagues (1999a) revealed that patients with schizophrenia were impaired in discriminating velocity difference between two moving gratings, while their ability to perceive contrast and orientation was spared. The motion-sensitive middle temporal area (MT, or V5) was implicated as a key brain region for the observed motion perception deficits in schizophrenia.

Recent studies have attempted to elucidate specific MT dysfunction by examining the center-surround mechanisms in schizophrenia, but the findings are still controversial (Tadin et al., 2006; see also Chen, Norton, & Ongur, in press). Many neurons within MT have antagonistic center-surround receptive fields and the ability to perceive motion is reduced as the size of a moving stimulus increases in healthy people (Tadin, Lappin,

Gilroy, & Blake, 2003). Interestingly, a relatively smaller threshold increase with increasing stimulus size was observed in schizophrenia patients, reflecting weaker center-surround suppression in MT (Tadin et al., 2006). The weakened center-surround antagonism was also correlated with negative symptoms, implicating a possible link with impaired social functioning in schizophrenia. A more recent study, however, reported that the center-surround suppression in schizophrenia patients became stronger when global motion (random dots) was presented on the surround receptive fields (Chen et al., in press), suggesting that motion perception is dependent upon different types of stimuli in schizophrenia.

Indeed, a patient's motion perception is dependent upon types of motion (Chen et al., 2003b). Physiological studies on MT functions further support that different kinds of motion can affect perception in different ways: Motion processing in some part within area MT is similar to that in primary visual cortex, such that it focuses on the local signals, whereas other parts of MT mainly process global motion signals (Born & Tootell, 1992). These structural and functional characteristics of the cells within MT indicate that neural units at the global stage can integrate dispersed local motion signals with their target receptive field size (Sclar, Maunsell, & Lennie, 1990). Generally, psychophysical studies report that schizophrenia patients are deficient in perceiving global motion, but are relatively intact in simple detection of local motion. This observation implicates that parts of MT involved in global perception may be compromised in schizophrenia.

To summarize, a series of studies on motion perception in schizophrenia suggest that the deficits are selective in that: 1) they are associated with the velocity component of

motion signals as indicated by poor discrimination of velocity difference, and 2) are specific to global motion, not local motion stimuli in detection. Dysfunction within the motion sensitive area MT is strongly implicated for this deficient perception of motion in schizophrenia.

Visual perception and social functioning in schizophrenia

Although more precise mechanisms underlying these visual deficits are yet to be discovered, researchers have not only stayed within the field of perception. There also have been attempts to find possible impacts of visual deficits on a patient's daily life by investigating the possible link with one's social perception and cognition. Social perception and cognition refer to the process involved in how people perceive and interpret information about themselves, and other people in various social situations. For example, Sergi and Green (2002) measured schizophrenia patients' aptitude for social perception using the Half-Profile of Nonverbal Sensitivity (PONS, Rosenthal, Hall, DiMatteo, Rogers, & Archer, 1979). PONS requires subjects to assign situational labels to brief videotaped scenes of facial expressions, gestures, and voice intonations. They found a negative correlation between social perception and visual backward masking effect. Another recent study reported that schizophrenia patients' ability of theory of mind, or an ability to attribute beliefs, intentions, and feelings to other people and themselves (Frith, Morton, & Leslie, 1991; Premack & Woodruff, 1978), was correlated positively with their performance on a global motion perception task (Kelemen et al., 2005). These findings, therefore, suggest that perceptual deficits may influence one's social behaviors. In this manner, investigation of the relationship between perceptual

ability and social functioning in schizophrenia is an important issue in that it could provide some clue for the way basic perceptual abilities may affect higher-level cognitive functions and behavioral outcome. Furthermore, findings may provide useful information for diagnostic assessment of schizophrenia, eventually contributing to a strategy for more efficient treatment.

However, simply observing correlations has its limitations. The causal relationship is unclear, and the visual stimuli widely used - moving gratings and random dot cinematograms (RDC) - are laboratory-specific and unnatural. An alternative way is to use another type of visual stimuli that is rich in social information by nature. Indeed, there have been several studies on a specific kind of motion that is meaningful especially in a social context, by providing input for identifying the actions and intentions of others (Blake & Shiffrar, 2007). This specific type of motion is termed "biological motion". Perception of biological motion and its underlying neural mechanisms have already been extensively studied in healthy individuals since Johansson (1973) introduced "point-light (PL)" animations. However, these studies have not been extended to the study of biological motion in schizophrenia.

Perception of biological motion in schizophrenia

Biological Motion

Not only humans, but many species are very sensitive to motion signals generated by other organisms (e.g. Johansson, 1973; Oram & Perrett, 1994). Such perception of actions and intentions of others has a primary role in survival. It is also instrumental for developing social skills in our society, where we spend much of our time interacting with

others. In a classic study conducted by Johansson (1973), he demonstrated that observers are readily able to recognize extremely simplified human movement portrayed by PL animations that depict familiar human activities with only a couple of markers (dots) on the head and joints of the body. PL animations are particularly advantageous in terms of their lack of explicit representation of body shape. Instead, perception of body shape and activity is provided by the kinematic information in the spatiotemporal pattern of the markers. Subsequent studies using PL animations demonstrated that perception of biological motion is rapid (Johansson, 1976), specific to orientation (Bertenthal & Pinto, 1994; Sumi, 1984), easily recognized even in masking elements (Bertenthal & Pinto, 1994; Cutting, Moore, & Morrison, 1988), and extends to perception of gender (Kozlowski & Cutting, 1978) and social signals such as mood and intention (Loula, Prasad, Harber, & Shiffrar, 2005; MacArthur & Baron, 1983).

Given this significance and efficiency of biological motion perception, it has been suggested that a visual system has developed a specialized mechanism for effortless and efficient processing of such biological motion signals. Indeed, even infants 4 to 6 months of age are known to exhibit a preference for biological motion patterns, suggesting that perception of biological motion may be an intrinsic capability of the visual system (Fox & McDaniel, 1982). Furthermore there exists highly confirmative evidence of underlying neural correlates that seem to be different from the mechanisms involved in processing non-biological, general motion. For example, two case studies reported an interesting double dissociation in people with selective brain damage. Two patients with lesions in the superior temporal sulcus (STS) normally detected coherent motion and recognized shape-from-motion, but these patients had difficulty recognizing human activities

portrayed in biological motion animations (Schenk & Zihl, 1997a,b). Complementary results has been reported in another case: a patient who had extensive damage in the extrastriate visual areas, including portions of the posterior parietal and temporal lobes, had impairment in detecting coherent motions in noise, speed discrimination, and shape defined by relative motions. But this patient could identify the actions portrayed by PL animations (Vaina, Lemay, Bienfang, Choi, & Nakayama, 1990). There is also physiological evidence for neurons that selectively respond to biological motion. Some cells in the anterior portion of the superior temporal polysensory area (STPa) of macaque monkeys were sensitive to primate forms and movements (Perrett, Harries, Mistlin, & Chitty, 1990) and to the biological motion represented in PL animations (Oram & Perrett, 1994). Human imaging studies have identified robust activation within the posterior superior temporal sulcus (STSp) associated with viewing PL biological animations, using PET (Bonda, Petrides, Ostry, & Evans, 1996) and fMRI (Grossman et al., 2000). Subsequent studies additionally revealed that STSp activation depends on the orientation of the PL sequence (i.e. upright versus inverted) (Grossman & Blake, 2001) and depends on whether observers were able to recognize a PL sequence embedded in masking noise as human after perceptual learning (Grossman, Blake, & Kim, 2004).

Perception of biological motion, in addition to other types of visual perception associated with earlier stages of visual processing, is a specifically important aspect of visual perception. It is also very meaningful within social context by its nature. Therefore, it is necessary to consider the relationship between perception of biological motion and social functioning, and their common underlying neural mechanism.

Social functioning in schizophrenia and the role of the STS region

It is already well established that schizophrenia patients show impairments of social functioning. They are impaired in perceiving and interpreting socially-relevant stimuli. For example, they have deficits in face perception, emotional processing, theory of mind, and self-processing (Grady & Keightley, 2002). Past studies consistently reported abnormalities in a broad range of social cognition/perception tasks in schizophrenia: patients show poorer performance on tasks of judging the direction of eye-gaze (Phillips & David, 1997) and on face processing regardless of emotional expression on faces compared with healthy controls (Williams, Loughland, Gordon, & Davidson, 1999; Gaebel & Wölwer, 1992; Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000). Impaired ToM, the ability to mentalize, has also been demonstrated in schizophrenia patients, as well as, in children with autism (Corcoran, Mercer, & Frith, 1995; Frith & Corcoran, 1996). All of these social dysfunctions in schizophrenia have been regarded as trait, rather than state-dependent, abnormalities preceding the onset of the illness and also even enduring after reduction of clinical symptoms (Brüne, 2003; Edwards, Pattison, Jackson, & Wales, 2001). Some studies, however, have argued that ToM impairment might be associated with symptom severity or IQ (e.g. Pickup & Frith, 2001).

Structural and functional imaging studies have attempted to identify the anatomical and functional neural basis for social cognition including ToM. These imaging studies have further explored brain areas including the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), the superior temporal cortex (STC), and the amygdala (Allison, Puce, & McCarthy, 2000; Burns, 2006).

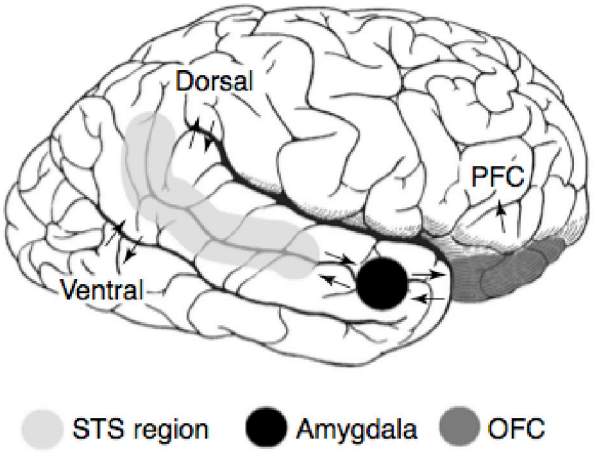

Figure 1. The brain structures important for social perception and cognition. The STS region (STS, adjacent cortex on the surface of the superior and middle temporal gyri, and cortex on the surface of the angular gyrus) has reciprocal connections with the amygdala, which in turn is connected to orbitofrontal cortex. The OFC is connected to the prefrontal cortex, which in turn is connected to mortor cortex and the basal ganglia. STS cells responsive to body movements and biological motions are mainly located at the posterior part of the STS region *(Adapted from Allison et al., 2000, Fig. 7.)*.

It is worth noting that the role of the STS region has been emphasized in studies on social perception and cognition (Allison et al., 2000). In addition to body movement (i.e. biological motion), cells in the STS region in monkeys are also vigorously responsive to movement of head (Hasselmo, Rolls, Baylis, & Nalwa, 1989), mouth (Puce & Allison, 1999), and hand (Bonda et al., 1996; Grèzes, Costes, & Decity, 1999), all of which are crucial for communication, especially when those movements are socially meaningful. Similar findings were reported in human studies using PET (Wicker, Michel, Henaff, & Decety, 1998) and fMRI (Puce, Allison, Bentin, Gore, & McCarthy, 1998). The STS region shows activation to cartoons and stories requiring ToM, but is not activated by stories not requiring ToM (Gallagher et al., 2000). The STS region, therefore, can be regarded as one of the critical brain areas for the further understandings of visual perception and its interaction with higher level cognitive, specifically social cognitive

functions in both schizophrenia patients and healthy people. Specifically, the STS region 1) belongs to the visual system, receiving input from both the dorsal and ventral visual pathways. Therefore, the STS region may act as an interface between the two pathways (Karnath, 2001), 2) is crucially involved in processing a wide range of social cues, and 3) is reciprocally connected with frontal cortices, implicating its influence on cognitive functions. As previously mentioned, schizophrenia patients' performance on biological motion tasks has not yet been studied until now. Biological motion is a suitable visual stimulus to augment the understanding of visual deficits and its possible relationship with impaired social functioning in people with schizophrenia. Considering the importance of the STS region for both functions, it is reasonable to expect that schizophrenia patients may have a difficulty processing biological motion stimuli, which is the main question of this dissertation. This hypothesis is further supported by a structural imaging study that reported a partial volumetric reduction in the anterior portion of the superior temporal cortex (Shenton et al., 1992).

Summary and Purpose of the study

Summary and importance of the study

Past studies on visual perception in schizophrenia have revealed that patients are impaired in processing visual stimuli requiring functions of the dorsal visual pathway as evidenced by prolonged visual backward masking effect (e.g. Green et al., 1994a,b), impaired velocity discrimination (Chen et al., 1999) and deficient global, coherent motion perception (e.g. Chen et al., 2003). Physiological findings also provided evidence of an abnormality along the dorsal visual pathways (e.g. Butler et al., 2001) in schizophrenia.

Recent studies have attempted to find a possible link between visual perception and social functioning in schizophrenia (Sergi & Green, 2002; Kelemen et al., 2005). However, research on perception of biological motion, which is important for appropriate social interaction, has not been conducted in schizophrenia patients, despite considerable findings in healthy individuals. Therefore, investigating how schizophrenia patients process these socially-meaningful motion stimuli is the primary purpose of this dissertation.

The importance of this study can be summarized in the following manner. First, in addition to past findings on various cognitive and perceptual dysfunctions, this study will make it clear whether patients with schizophrenia would have another kind of deficit that is related with both perceptual and social abilities. This finding will add a new observable behavioral abnormality to known deficits, and therefore, will augment our understanding of behavioral outcome in schizophrenia. Second, in the context of motion perception, investigating biological motion perception in schizophrenia will be helpful in determining whether the deficits in motion perception are restricted to a specific type of stimuli (e.g. coherent, translational motion) or extends to ecologically familiar motions. Past case studies have suggested that processing non-biological motion and biological motion might depend on different mechanisms (e.g. Vaina et al., 1990); however, it is still unclear whether the patients would have an extended deficit caused by abnormalities in early visual processing or have another kind of impairment which has not been reported. In addition, there are some ambiguous aspects in studies on biological motion perception in healthy people. For example, recent findings strongly suggest that both bottom-up and top-down processing are involved in biological motion perception (Johansson, 1973;

1975; see also Bertenthal & Pinto, 1994; Thornton, Pinto, & Shiffrar, 1998). However, more specific influence of those processes on biological motion perception remains to be examined. By comparing performance of healthy people with schizophrenia patients on biological motion tasks, we will be able to clearly define what "normal" perception of biological motion is, as well as what process is aberrant in patients with schizophrenia. These finding will contribute to both research fields of normal perception and perception in mental disorders. Third, as "socially-relevant" stimuli, biological motion perception in schizophrenia would provide a clue for further understanding of impaired social functioning and its possible perceptual manifestation. In other words, it is possible that putatively impaired biological motion perception and social dysfunction could co-occur or be correlated with each other. If so, impaired biological motion perception would also work as a reasonable marker for social dysfunction in schizophrenia. Fourth, past research on social perception/cognition has identified brain regions of the OFC, the STS, and the amygdala and the functional connectivity among them as the "social-brain" (Burns, 2006). However, precise functional connectivity among these areas are yet to be elucidated in the normal brain. Furthermore, possible functional abnormalities in these regions in schizophrenia remain to be examined. A functional imaging study on biological motion perception will provide more information on the functional operations within the STS area. The imaging study will also provide a basis for further studies on the social-brain areas extending to the frontal cortex and amygdala, and on their functional connectivity in both healthy people and schizophrenia patients.

The fMRI study on biological motion perception has another advantageous aspect: it is well known that schizophrenia patients are impaired in motion perception (e.g. Chen et

al., 1999a,b) as previously mentioned, and area MT has been implicated for the deficits (e.g. Tadin et al., 2006). Past imaging studies on area MT in schizophrenia have mainly focused on activation within this area that is associated with smooth-pursuit eye movements (SPEM) using simple eye tracking tasks (Hong et al., 2005; Lencer, Nagel, Sprenger, Heide, & Binkofski, 2005). So the possible group difference between schizophrenia patients and controls in MT activation to complex motion stimuli is still not clearly known. The fMRI study will reveal MT activation, as well as STS activation to PL biological motion and will inform us as to whether the activations to biological motion are correlated in these regions. Therefore, the fMRI study will provide further insight into schizophrenia patients' abnormal visual system in addition to social-brain.

Goals and hypotheses

To answer these broad questions, this dissertation included a series of tasks using psychophysical and functional imaging methods containing specific goals and hypotheses for each task. The first goal is to explore whether schizophrenia patients have impairment in perceiving biological motion. This possible impairment is examined with a simple discrimination task. Schizophrenia patients were expected to have worse sensitivity in discriminating biological motion compared to healthy controls, based on past perceptual, social, and anatomical evidence. The second goal was to confirm the deficit in biological motion perception of patients using additional behavioral tasks that require different aspects of perceptual abilities, such as detection. If the deficit in biological motion perception is robust in schizophrenia, it would be also observed regardless of the tasks. The third goal is to confirm whether biological motion perception is associated with

social functioning in both schizophrenia patients and healthy controls. For this part, group difference in assessed social functioning is examined. Correlation between assessed social functioning and performance on biological motion tasks is also investigated. Decreased social functioning was expected to be associated with poorer performance on biological motion tasks. The fourth purpose is to identify neural correlates underlying deficits in biological motion perception using the fMRI method with particular focus on the posterior STS region. The fMRI study also provides more information on normal STS activation to biological motion in healthy controls. Whether or not schizophrenia patients' impairment in general motion perception affects their biological motion perception is also examined by additionally observing functional activation to biological motion within the motion-sensitive area MT.

There is one more purpose of this dissertation. I felt it worthwhile to investigate visual perception, including biological motion perception, in patients with another kind of mental disorder that has some overlapping symptomatic and cognitive characteristics with schizophrenia. A previous study has already reported that children with autism have impairment in perceiving biological motion (Blake et al., 2003). As is widely known, autism is also characterized by its severely compromised social functioning (e.g. impaired ToM). Therefore, it is important to examine whether the deficits in biological motion perception could be a widespread deficit among mental disorders sharing common characteristics. OCD and schizophrenia appear to be quite different mental disorders explicitly. However, some OCD patients have schizotypal personality and similar cognitive dysfunction to schizophrenia. In addition, OCD patients also suffer from their impaired social functioning, and past studies implicate possibilities of

abnormal visual perception in this population. As an expanded study, therefore, patients with obsessive-compulsive disorder (OCD) were also recruited and tested on a series of visual tasks. More details and background on OCD are addressed in CHAPTER V.

CHAPTER III

PERCEPTION OF BIOLOGICAL MOTION IN SCHIZOPHRENIA: BEHAVIORAL STUDY

Introduction

As reviewed in CHAPTER II, previous psychophysical and physiological studies on visual perception in schizophrenia have mainly focused on the functioning along the dorsal visual pathway, and revealed that patients with schizophrenia generally have difficulty performing visual tasks that require rapid, dynamic visual stimuli, which includes prolonged VBM effect (Green et al., 1994a,b), deficient velocity discrimination (Chen et al., 1999a,b), impaired global motion perception (Chen et al., 2003b), and aberrant VEP along the dorsal scalp sites (Butler et al., 2001; 2005). Another line of research on schizophrenia has revealed poor social functioning, including a deficient ability to perform ToM tasks, in schizophrenia. Social signals are thought to be processed within neural circuitry consisting of orbitofrontal cortex, amygdala and STS. STS is the region of interest in the present study because this region works as an interface between the dorsal and ventral visual pathways (Oram & Perrett, 1996) and is very sensitive to social signals including socially-meaningful movements (Allison et al., 2000).

Therefore, CHAPTER III focuses on schizophrenia patients' ability in perceiving biological motion by describing a series of behavioral tasks that use various familiar human activities portrayed by point-light (PL) animation sequences. In experiment 1, schizophrenia patients and controls were tested on a simple task of discriminating biological motion from non-biological, scrambled motion. A static global form task was

added to rule out the possibility of general deficits of global integration in schizophrenia. In experiment 2 and 3, the deficits in biological motion perception were further examined with a detection task, and another discrimination task requiring more fine discrimination, respectively.

Experiment 1: Discrimination of biological motion from scrambled motion

The purpose of experiment 1 was to explore whether patients with schizophrenia have difficulty perceiving biological motion when compared to matched healthy controls. Specifically, the ability of distinguishing biological motion from non-biological, scrambled motion was investigated using a discrimination task. Since biological motion is thought to be also meaningful in social contexts, the relationship between perception of this type of motion and participants' general social functioning was also examined. If patients with schizophrenia show a deficit in discriminating between biological motion and non-biological motion, it is possible that this deficit may merely a general deficit in visual processing. Therefore, an additional difficult perceptual grouping task (global-form task) was conducted, which requires participants to detect global form against background noise. The global form task allows us to assess the motivational and attentional state of the participants. Furthermore, this task provides additional evidence for relatively spared visual information processing when processing motion signals is not required (e.g. O'Donnell et al., 1996).

Methods

Participants

Fourteen outpatients (5 females and 9 males), who met the criteria for schizophrenia or schizoaffective disorder of the Diagnostic and Statistical Manual of Mental Disorder – 4th edition (DSM-IV) (American Psychiatric Association, 1994), were recruited from the outpatient clinic of Vanderbilt Psychiatric Hospital in Nashville, TN. Diagnosis was determined on the basis of the Structured Clinical Interview for DSM-IV (SCID) (Spitzer & Williams, 1985). The mean age of the patients was 38.3 years (SD = 7.8 years), the mean education level was 12.6 years (SD = 2.0 years), and their mean illness duration was 14.5 years (SD = 8.7 years). All patients were taking atypical antipsychotic medication at the time of testing, which includes risperidone, clozapine, or olanzapine. The CPZ dose (dosage equivalent to chlorpromazine) was calculated (Bezchlibnyk-Butler & Jeffries, 1999). Clinical symptoms at the time of testing were assessed with the Brief Psychiatric Rating Scale (BPRS, Overall & Gorham, 1962). Positive and negative symptoms were assessed using the Scale for Assessment of Positive Symptoms (SAPS, Andreasen & Olsen, 1982) and the Scale for Assessment of Negative Symptoms (SANS, Andreasen & Olsen, 1982), respectively. The mean BPRS score was 28.3 (SD = 11.7). The mean SAPS and SANS scores were 30.8 (SD = 20.2) and 30.9 (SD = 20.7), respectively.

Fifteen healthy controls (9 females and 6 males) were recruited from the local community through advertisements. Participants were excluded if they had: (1) past or present DSM-IV Axis I or Axis II disorder or (2) a family history of psychotic illness. In addition, the exclusion criteria for all participants were (1) current substance use, (2) a

history of brain injury or seizures, (3) a neurological disorder, and (4) mental retardation. The mean age of healthy controls was 36.6 years (SD = 11.8 years) and their mean education level was 13.5 years (SD = 2.3 years), these values were not significantly different from those of the patient group. Control participants were also screened to rule out schizotypal personality using the Schizotypal Personality Questionnaire (SPQ, Raine, 1991) before the experiment. The SPQ is a 74 item true-false self-report questionnaire that assesses syndromes of schizotypal personality. According to Raine's data, 10% of the population scored above 41, and those individuals may have an elevated risk for schizotypal personality disorder. The mean of control participants in this study on SPQ was 18.1 (SD = 11.1), which is well below the cut-off score published by Raine (1991). All participants had normal or corrected-to-normal (eye glasses or contact lens) vision. They were provided with a complete description of the procedure and gave written consent. The experimental protocol was approved by the Institutional Review Board of Vanderbilt University. All participants were paid for their participation in the study.

Assessment of social functioning

For all participants, general social functioning was assessed with the Zigler social competence scale, which was calculated using a demographics questionnaire filled out before testing (Zigler & Levine, 1981). Each variable on the scale was divided into three categories, ranking from low (zero) to high (two points). Variables used to calculate the Zigler score are education level (less than 8^{th} grade, 8^{th} grade up to completion of high school, one year or more of college), occupation status (unskilled, semi-skilled, skilled), employment history (almost none, part-time, almost all), and marital status (never

married, separated or widowed, continuously married). Then they were summed to yield a total score. An overall low score, therefore, suggested reduced social functioning.

Table 1. The demographic data

	Control subjects (n = 15)	Schizophrenic subjects (n = 14)	*p*
Age	36.6 (11.8) [A]	38.3 (7.8)	n.s.
Education (years)	13.5 (2.3)	12.6 (2.0)	n.s.
WASI IQ Score [B]	95.7 (15.0)	95.0 (12.6)	n.s.
BPRS	n/a [C]	28.3 (11.7)	
SAPS	n/a	30.9 (20.7)	
SANS	n/a	30.8 (20.2)	
SPQ	18.1 (11.1)	n/a	
Handedness (L/R/Ambi)	1/14/0	0/13/1	
CPZ equivalent [D]	n/a	290.8 (143.9)	
Illness duration (years)	n/a	15.0 (8.39)	
Zigler score [E]	5.9 (1.8)	2.5 (1.3)	* < .01

[A] Mean (standard deviation)
[B] Wechsler Abbreviated Scale of Intelligence ™
[C] Not applicable
[D] Chlorpromazine dose equivalent (mg/day)
[E] Zigler Social Competence Scale (Zigler and Levine, 1981)

Apparatus and Procedure

Displays were presented on a TFT-LCD monitor of a Macintosh computer (Power Mac G3). And the biological motion task was controlled with an application program and the global form task was created in Matlab© with the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). All experiments were conducted in a dark room illuminated by light from the video screen. In both the biological motion task and the global-form task, all stimuli appeared black against a gray background.

Biological Motion task: The biological motion stimuli were various kinds of human activities portrayed by PL animations. The same stimuli were used in a previous study (Blake et al., 2003). These stimuli were created in the following way: Twenty-four

familiar activities, including running, kicking, climbing, throwing and jumping, were captured by video-recording as an adult engaged in those activities. Video clips were then imported to a computer to create biological motion stimuli. Markers (dots) were placed on the joints (head, near shoulder, elbows, wrists, hip, both knees and ankles) in each frame of the sequence to produce successive frames. These successive frames were converted to matrices that could be manipulated and animated in Matlab© and an application was created with Macromedia (Adobe Inc. San Jose, CA). The dots were always visible except when they would be occluded by other parts of the body. An example of several (not completely successive) frames from a 'walking' biological motion sequence is shown on the left in Fig. 2. Frames on the right in Fig. 2 show a series of a phase-scrambled version of the 'walker'. A series of scrambled motion sequences was created from the normal biological animations and, therefore, consisted of the same individual dots undergoing the same local motions as the corresponding biological counterparts. Scrambling was produced by randomizing both the temporal phases (shifting frames) and the spatial locations (initial positions) of the dots in a given animation, thereby perturbing the hierarchical, pendular motions that are characteristics of biological motion. Each animation lasted 1 s. The size of each dot was approximately 12 arc min, and the average speed within a sequence was 4 °/s. The visual angle of each sequence was approximately 7 ° at viewing distance of 57cm.

The observer's task during a trial was to judge whether a series of briefly presented animations depicted biological or scrambled motion. Before testing, the task was described in detail to each subject and examples of biological and scrambled animations were shown to the participants. To make sure that participants understood the task, they

were instructed to make an oral response to the examples. Then a series of 100 trials were presented with each entailing the brief presentation of either a biological sequence or a scrambled sequence. There were 50 biological animations and 50 scrambled motion sequences and the order of trials was randomly determined. Following each trial, the subject indicated whether or not the animation portrayed human activity by pressing one of two pre-assigned keys on the computer keyboard; auditory feedback was provided after each trial. There was no time limit to respond, and the observer pressed a spacebar to move on to the next trial. All patients and controls successfully finished this task, which lasted 8 to 15 min depending on each individual's pace.

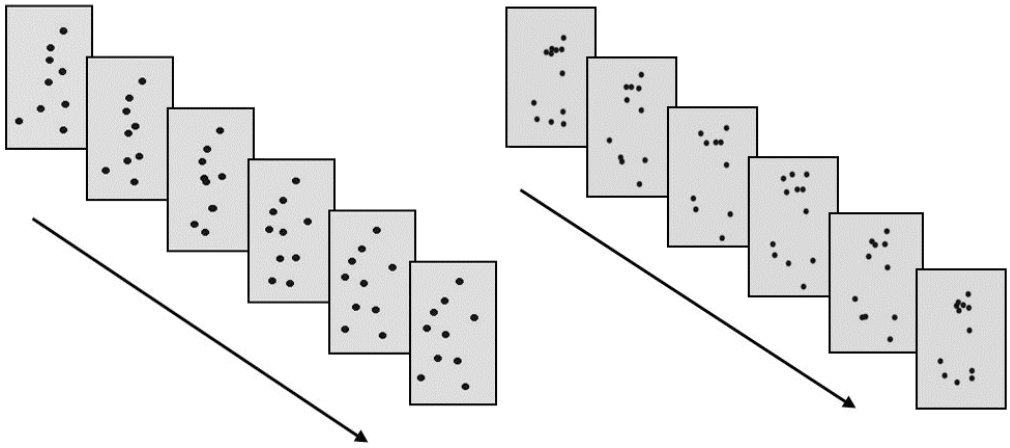

Figure 2. Examples of stimuli used in the biological motion task: Frames on the left show normal biological activity (walking) from quasi-successive point-light animation sequences. Scrambled motion frames (right) are the corresponding counterparts of the biological sequences on the top, containing the same dots undergoing the same local motions, only spatiotemporal phases were scrambled to generate nonbiological motion.

To derive an index of performance on this task, the number of (1) hits ("biological" responses to biological motion sequences) and (2) false alarms ("biological" responses to

scrambled sequences) were counted. Then the hit-rate and false alarm-rate were used to calculate the statistic of an unbiased measure of sensitivity or the difference between the *z*-transforms of the hit-rate and false-alarm rate, *d′*, which is expressed as:

$$d' = |z(\text{hit rate}) - z(\text{false alarm rate})|.$$

Global form task: The global form task was a four-alternative forced choice task, which measured participant's ability to group small, stationary line elements into a larger, global form. The screen of the computer monitor was divided into four equally-sized quadrants whose boundaries were delineated by thick black lines, and the entire screen was filled with short lines most of which were oriented randomly. Each line subtended a visual angle approximately 30 min. length × 2 min. width. In one of the four quadrants, a small group of six lines formed a quasi-circular shape within a randomly selected region of the quadrant. The probability of the appearance of the quasi-circular shape in any of the quadrants was equal over the trials. Since the lines forming the shape were the same in color and size as the other distracter lines, the only cue for detecting the target was the spatial arrangement termed "good continuation" in the Gestalt tradition. Difficulty of each trial was manipulated by changing the clarity of the target. To do this, '*jitter*' was applied to the orientation of each line segment forming the quasi-circular shape; jitter comprised an angular deviation among target contours from the canonical value specified by their positions on the circle. Larger degrees of jitter made it more difficult to detect the target, thereby participants had difficulty designating in which quadrant it appeared. Displays remained visible until the subject responded. Viewing distance was the same as that of the biological motion task (57cm), and the visual angle of the target was approximately 2.5 °. Examples of the displays are shown in Fig. 3.

The observer's task was to locate the quasi-circular shape that looked like a 'stop-sign' and to indicate in which quadrant it appeared. They indicated the quadrant by pressing one of four keys assigned to each quadrant (top left, top right, bottom left or bottom right). There was no practice trial or presentation of a sample stimuli before the formal testing. However, the test began with a series of trivially easy trials (i.e. jitter = 0, see Fig. 3 top) so that each subject quickly became accustomed to the task. The degree of jitter over trials was adjusted by a 1-up/1-down staircase procedure to find the level of jitter at which the subject could identify the location of the target with greater than 70% accuracy. Thus, the target became more difficult to detect following correct answers and less difficult following incorrect answers. Visual feedback showing the correct location was provided after each trial. The total number of trials was 100, and the mean and standard deviation of the jitter from the last 8 trials of the staircase were recorded as the estimate of the threshold. The subject could rest at any time during trials.

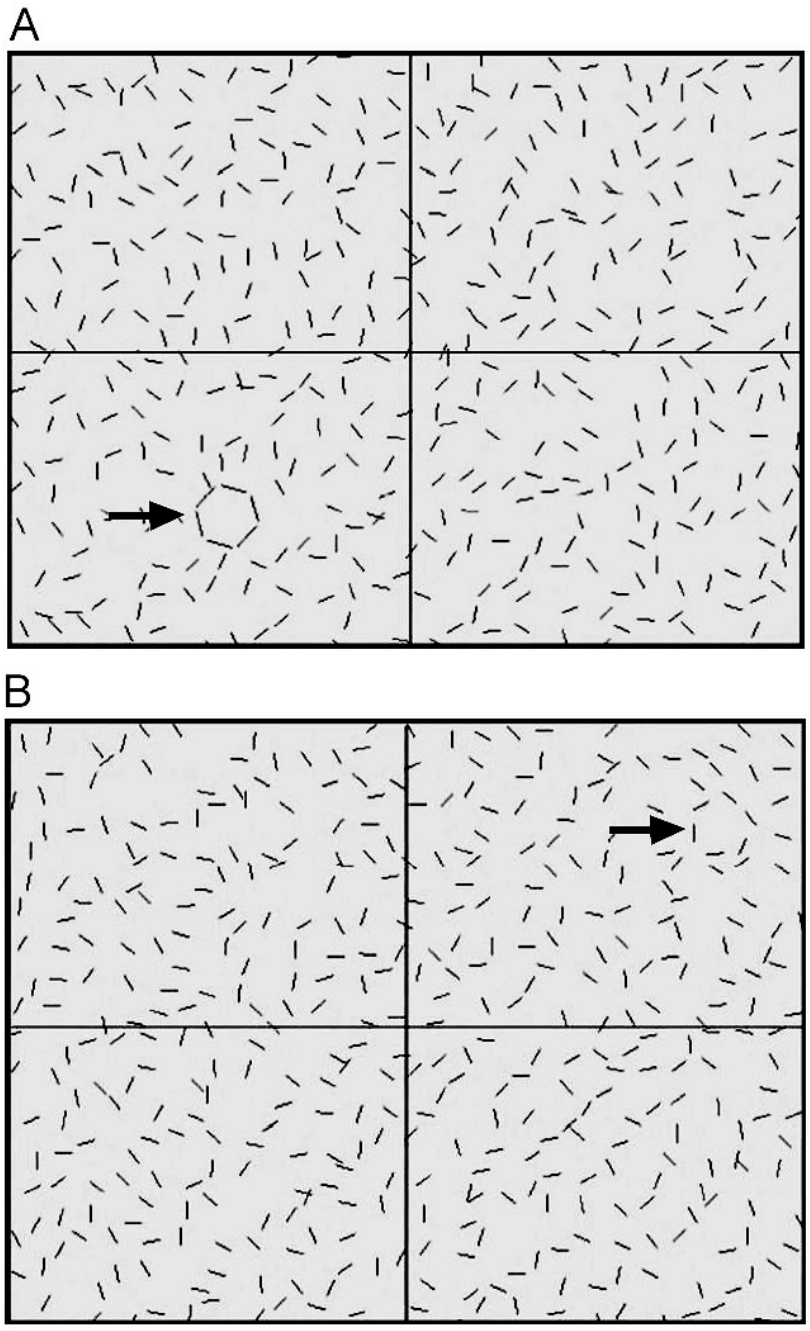

Figure 3. Examples of the global form task. The target was a quasi-circular shape formed by a small group of six lines. The difficulty of the target was adjusted by varying jitter, the angular deviations among target contours from the canonical values, according to a staircase procedure. In example A, the target is easily recognized at the lower-left quadrant (see arrow). Example B shows more difficult trial in which the target is less clear.

Results

Biological motion task Mean *d′* values and standard error of means (SE) in schizophrenia patients and healthy controls are shown in Fig. 4. Discrimination of biological motion in the patients group was worse than in the control group (*d′* = 2.21 (0.40) vs. 2.80 (0.84)), with the difference between the two groups being statistically significant (t (27) = 2.41, $p = 0.023$).

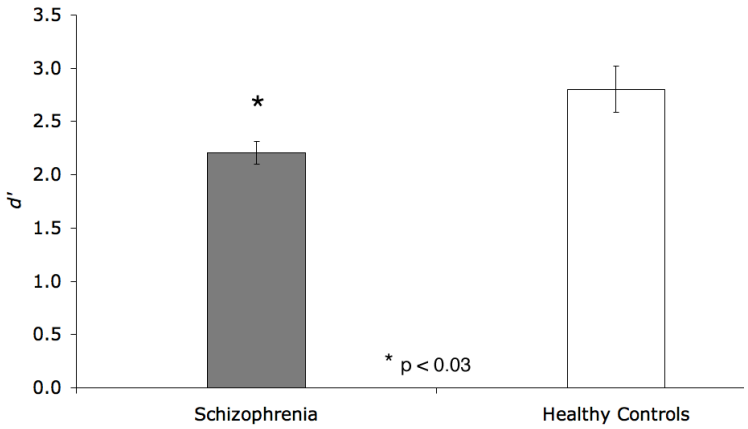

Figure 4. *d′* values in the two groups. Error bar shows 1 standard error of means (SE).

Because the sensitivity of *d′* indicates the distance between the signal (hit-rate) and the signal + noise (false alarm), it does not tell whether its lower value was caused by low hit-rate or higher false alarm-rate or both. Fig. 5 shows mean (SE) hit-rate and false alarm rate in the two groups. Schizophrenic patients and healthy controls were not significantly different in hit-rate (89.42 (1.82)% vs. 90.93 (1.37)%) while the patients' mean false alarm-rate (19.71 (2.20)) was higher than that of controls (11.06 (2.08)). Difference in false alarm-rate was statistically significant (t (27) = 2.85, $p < 0.01$), indicating that

patients with schizophrenia have a stronger tendency to judge scrambled motion as biological motion, resulting in the lower value of *d′*.

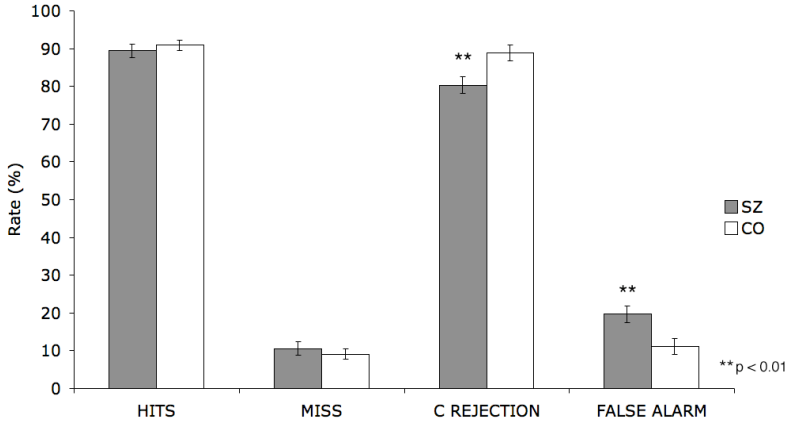

Figure 5. Mean (SE) hit-rate and false alarm-rate in the two groups. SZ: schizophrenia, CO: controls. C REJECTION: correct rejection

Global Form task Mean (SE) jitter threshold values in the two groups are shown in Fig. 6. Jitter threshold (deg) in the patients group was comparable to that of healthy controls ($t(27) = 1.19$, $p = 0.24$); the patients' mean jitter threshold was 16.9 (SE = 3.74) and 18.5 (SE = 3.42) in control group.

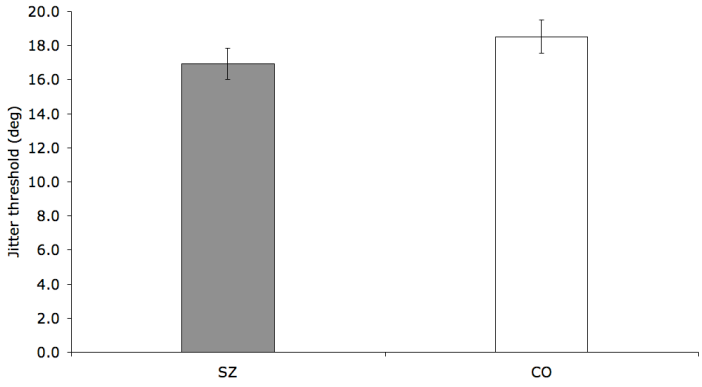

Figure 6. Mean (SE) angular jitter thresholds on the global-form task.

Correlations with symptoms and social functioning The correlation between *d′* values and overall symptom severity measured by BPRS, positive and negative symptoms (SAPS and SANS scores) were examined for the schizophrenia group. No significant correlation was observed. Furthermore, *d′* was not significantly correlated with medication (CPZ dose equivalent), either.

For all subjects, significant correlation was observed between *d′* values and general social functioning measured by the Zigler social competence scale (Fig. 7) ($r = 0.707$, $p < 0.001$, n = 29). Furthermore, the group difference in Zigler scores was also significant ($t(27) = 5.84$, $p < 0.001$). Within the control group, *d′* and Zigler score was significantly correlated, as well ($r = .712$, $p < 0.01$, n = 15). Although the correlation within the schizophrenia group did not reach significance ($r = 0.43$, $p = 0.12$, n = 14), those subjects with impaired social functioning (as indicated by low Zigler scores) tended to have worse performance on the biological motion task.

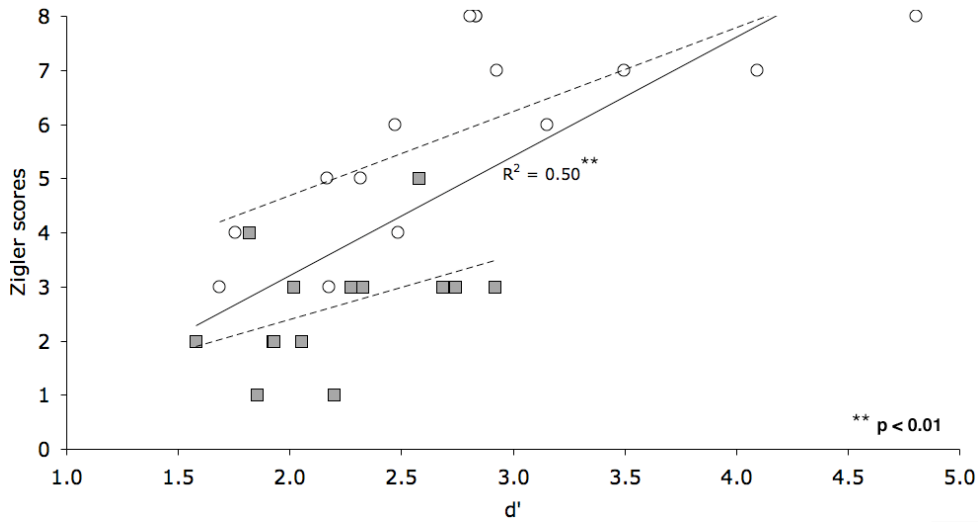

Figure 7. Correlation between *d′* and scores on Zigler social competence scale. Squares: schizophrenia patients, Circles: normal controls. Solid line: regression line for all participants data, Dotted lines: regression lines within each group.

The same correlations were examined on the global-form task. Performance of the patients on the global-form task did not correlate with BPRS, SAPS, SANS scores, illness duration, CPZ equivalent or Zigler scores. In the control group, no significant correlation was observed between jitter threshold and Zigler scores.

Discussion

Experiment 1 explored possible deficits in perceiving biological motion in patients with schizophrenia by investigating their ability to discriminate between biological motion and scrambled, non-biological motion in comparison to performance in the healthy control group. The ability to integrate local elements into a global shape was also examined on the global-form task. The results revealed that patients with schizophrenia showed a deficit in recognizing biological motion portrayed by PL animation sequences compared to control participants. On the other hand, the patients' performance on the global-form task was comparable to that of control participants.

The global-form task was difficult and challenging. It should be noted that there were only six small lines that were indistinguishable from the other numerous "noise" lines, and the only cue for target detection was their spatial arrangement. Normal performance on this task, therefore, suggests that the patients were able to maintain their motivation and attention on a perceptually difficult task. Results from the global-form task further support the notion that visual processing in schizophrenia is relatively intact when the functions of the transient visual channels (i.e. dorsal visual pathway), including motion processing, are not required. Consistent with this interpretation, Chen et al.

(1999a) showed that orientation discrimination and contrast detection were spared in schizophrenia. Similarly, O'Donnell et al (1996) found that patients with schizophrenia processed form attributes such as high spatial frequencies and patterns just as well as controls. The neural interconnections among orientation-selective neurons at early visual processing stages, including the primary visual cortex (V1) (Gilbert, 1993), are thought to be involved in the integration of contour information for perception of targets in displays similar to those used in this experiment (Field, Hayes, & Hess, 1993). Therefore, the results suggest that the patients' impaired biological motion perception is not explained by general abnormalities of the primary visual cortex.

As mentioned in the introduction, a posterior region located in and around the superior temporal sulcus (STSp) is known to be strongly and selectively activated by biological motion signals (Jellema & Perrett, 2003; Perrett et al., 1990; Oram & Perrett, 1994). Therefore, it is natural to hypothesize that impaired biological motion processing found in this experiment may arise from functional deficits within the superior temporal cortex. However, it is difficult to reveal detailed neural mechanism with the current results.

One could argue that impaired biological motion perception may be another manifestation of the deficits in motion perception that already have been observed in people with schizophrenia, thereby arguing that dysfunction of the middle temporal area (MT) may account for the deficits in biological motion perception. This is not an implausible argument. Indeed, from earlier works, we know that patients with schizophrenia have no trouble perceiving "local" motion, where "local" refers to linear contours moving in a single direction (Chen et al., 2003b). However, patients do

experience difficulty integrating local motion signals to achieve a sense of global, coherent translational motion (Chen et al., 2003b), a task thought to involve area MT of the dorsal stream visual pathway (Born & Tootell, 1992). Therefore, it is possible that impaired biological motion perception is caused by patients' difficulty with "global" motion; after all, biological motion also requires integrating local motion signals over space and time. However, it is unlikely that MT is selectively involved in registering the hierarchical, pendular motions unique to the PL animations used in this experiment. Previous studies have revealed that MT equally responds to presentation of biological motion and global motion (Grossman et al., 2000; Howard et al., 1996). With this reason, MT does not seem to have the requisite sensitivity for discriminating between the two classes of animations.

In addition to a deficit in biological motion perception as indicated by significantly lower d' values in schizophrenia, the distribution of specific response patterns provides more information on the nature of the deficit. That is, as shown in Fig. 5, "hit" rates were comparable between the two groups. Interestingly, however, the patients' lower d' values are attributed to their higher "false alarm" rate, which indicates that patients have a strong tendency of misperceiving non-biological motion signals as biological, rather than having difficulty in processing biological motion signals themselves. This result suggests that the deficit of biological motion perception in schizophrenia may be qualitatively different from the impaired global motion perception. A growing body of work indicates that top-down processes may play an important role in the perception of biological motion (Bertenthal & Pinto, 1994; Cavanagh, Labianca, & Thornton, 2001; Dittrich, 1993; Thornton, Pinto, & Shiffrar, 1998). For example, Dittrich (1993) reported that the speed

and efficiency of biological motion processing could be strongly modulated by the category of the depicted action. Case studies of patients with extrastriate lesions sparing the temporal lobe have shown that an individual can lose the ability to perceive simple motion stimuli while retaining perception of biological motion, further implicating the role of high-level, top-down processing (McLeod, Dittrich, Driver, Perrett, & Zihl, 1996; Vaina et al., 1990). Therefore, patients' tendency of perceiving scrambled motion as biological indicated by higher false-alarm rate may reflect their abnormal top-down processing. To resolve these questions, it is necessary to conduct an additional experiment using functional imaging to observe neural activation within implicated brain areas in schizophrenia and healthy controls, which was done in the experiment described in CHAPTER IV.

Interestingly, children with autism showed a similar pattern of impaired biological motion perception but intact global form perception in previous study (Blake et al., 2003). An important characteristic of children with autism is impaired social functioning, specifically Theory of Mind (ToM), which is the ability to represent one's own and others' mental states. There is evidence that some patients with schizophrenia have impaired ToM, as well (Corcoran et al., 1995; Doody, Götz, Johnstone, Frith, & Owens, 1998; Frith & Corcoran, 1996; Pickup & Frith, 2001). In the present study, there was a clear group difference in general social functioning, and a significant correlation between Zigler score and d' was observed across all participants. Although social functioning was roughly estimated by the Zigler social competence scale and the ability of ToM was not measured, the significant correlation implicates that impaired biological motion

perception may be a behavioral sign related to impaired social functioning. At least these two could co-occur.

To summarize, the results of this study found that patients with schizophrenia have impairments in recognizing biological motion based on their misperception of non-biological motion as biological. This deficit may contribute to or coincide with some of the social dysfunction associated with schizophrenia.

Experiment 2: Detection of biological motion in schizophrenia

In experiment 1, the deficit of biological motion perception in schizophrenia was found for the first time using a task requiring discrimination between biological motion and scrambled motion. As the next step, it is necessary to investigate whether the deficit perceiving biological motion could be generalized into another aspect of visual perception, i.e. detection. Therefore, in this experiment, a more challenging task was used in assessing the ability to detect biological motion by superimposing PL animations on a field of moving noise dots. The task used a two-alternative, temporal forced-choice procedure, and the visual stimuli were similar to those used in several past studies (Bertenthal & Pinto, 1994; Bertenthal, Profitt, & Cutting, 1984; Thornton et al., 1998; Thornton & Rensink, 2002). Similar to widely used tasks of random-dot cinematograms (RDC) (Braddick et al., 2001; Chen et al., 2003b; Hiris & Blake, 1995; Newsome, Britten, & Movshon, 1989; Rizzo & Nawrot, 1998), the task in this experiment requires integration of motion information over space and time. Patients with schizophrenia might show a deficit caused by a failure of global integration of local motion elements (e.g. Chen et al., 2003b). However, converging lines of neurophysiological and imaging

evidence indicate that the neural processing of RDC and biological motion may be different (Blake & Shiffrar, 2007; Grossman et al., 2000; Sekuler et al., 2002), and the results from experiment 1 also showed that patients' poor discrimination was attributable to the misperception of non-biological motion rather than biological motion. In either case, patients with schizophrenia are expected to have difficulty detecting biological motion.

The correlation between performance on the detection task and general social functioning was also investigated. In addition, the "*Reading the Mind in the Eyes*" Task (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001) was administered, which assesses an adult's ability of theory of mind. Its relationship with biological motion perception was also examined.

Methods

Participants

Fifteen outpatients (7 females and 8 males) who met the criteria for schizophrenia or schizoaffective disorder in the DSM-IV (American Psychiatric Association, 1994) were recruited from the Outpatient Clinic of Vanderbilt Psychiatric Hospital, Nashville, TN. The exclusion criteria, including current substance use, brain injury, any neurological disorder, and mental retardation, was applied to the participants at the time of their visit. Diagnosis was determined on the basis of Structured Clinical Interview for DSM-IV (SCID) (Spitzer & Williams, 1985). Overall clinical symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS, Overall & Gorham, 1962), and positive and negative symptoms were assessed using the Scale for Assessment of Positive Symptoms

(SAPS) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen & Olsen, 1982), respectively. Mean BPRS score was 14.28 (SD = 10.13). Mean SAPS and SANS scores were 14.21 (SD = 11.66) and 19.85 (SD = 16.63), respectively. Thirteen healthy controls (7 females and 6 males) participated in the study through advertisement in the local community. The same exclusion criteria were applied to controls. In addition, control participants were excluded if they had any DSM-IV Axis I disorder, or a family history of psychotic illness. Controls were also screened to rule out schizotypal personality using the Schizotypal Personality Questionnaire (SPQ, Raine, 1991) before testing. Mean SPQ score in the control group was 14.5 (SD = 7.06). Group difference in age and education level was not statistically different, although close to significance (40.6±9.4 and 34.0±7.8, $t(26) = 2.02$, $p = 0.054$ in age, 14.4±1.7 and 15.9±2.1, $t(26) = 2.03$, $p = 0.052$ in education level). There was no difference in IQ (101.2±24.1 and 104.7±13.5, respectively, $t(26) = 0.44$, $p = 0.66$). General social functioning was also assessed using the Zigler social competence scale (Zigler & Levine, 1981) based on the participants' demographic information.

All participants had normal or corrected-to-normal vision, and they were provided a complete description of the procedure. The Institutional Review Board of Vanderbilt University approved the study protocol and consent procedure.

Table 2. The demographic data

	Control subjects (n = 13)	Schizophrenic subjects (n = 15)	*p*
Age	34.0 (7.8) [A]	40.6 (9.4)	n.s.
Education (years)	15.9 (2.1)	14.4 (1.7)	n.s.
WASI IQ Score	104.7 (13.5)	101.2 (24.1)	n.s.
BPRS	n/a [B]	14.28 (10.13)	
SAPS	n/a	14.21 (11.66)	
SANS	n/a	19.21 (16.63)	
SPQ	14.5 (7.06)	n/a	
Handedness (L/R/Ambi)	2/11/0	1/13/1	
Illness duration (years)	n/a	15.1 (8.5)	
Zigler score	5.9 (1.8)	2.5 (1.3)	< .001***
Eyes task [C]	25.3 (4.5)	19.5 (4.1)	< .01**

[A] Mean (standard deviation)
[B] Not applicable
[C] Revised version of the Reading the Mind in the Eyes Task. See text (Baron-Cohen et al., 2001). 10 controls and 12 patients were tested on this task.

Apparatus and Procedure

Biological motion detection task: The Biological motion task was presented on a CRT monitor (120Hz, TOTOKU Calix CDT2141A, Japan) controlled by a Macintosh computer (PowerMac G5, Apple Inc., Cupertino, CA). The task was controlled by Matlab© (Mathworks Inc. Natick, MA) and the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). The experiment was conducted in a dimly lit room illuminated by the computer screen only. The viewing distance was 64cm. The series of PL animations depicting human activities was created in the same way as described in experiment 1. Twenty-four scrambled motion sequences were also created by randomizing spatial locations of the 12 dots in each of the biological animations. The entire cluster of 12 dots defining a human or scrambled figure fell within a square region subtending approximately 7 ° on a side. The stimuli appeared as black against a white background.

This task used a two-alternative, temporal forced-choice procedure to assess detectability of biological motion superimposed within a field of moving "noise" dots.

On each trial, the participant viewed two successive, 1 s lasting intervals (separated by 0.5 s blank interval) in both of which a variable number of moving black dots appeared centered on a fixation point. In one of the intervals, a subset of the dots defined a PL biological motion activity, and in the other interval the scrambled version of that animation was presented. The interval – first or second – containing the biological motion sequence was randomly determined in each trial. In both intervals, a fixed number of noise dots were also presented. The noise dots had motions corresponding to motions of the dots defining the biological sequence presented on that trial for effective masking of the target. For example, dots defining a "walking" figure were also used to produce the noise dots that masked detectability of that figure. The locations of individual noise dots were spatially randomized within the virtual rectangular region within which all dots appeared. The dots defining the biological figure and those defining the corresponding scrambled set did not always fall at exactly the same location relative to the central fixation, but, instead, appeared anywhere within 80 pixels of the fixation. This spatial jittering maneuver made it impossible for participants to monitor just a small subset of dots to judge which interval contained the biological sequence. The difficulty of the task, therefore, varied directly with the number of noise dots presented. The size of each dot was 5-arc min, and the average speed within a sequence was 4 °/sec. The entire array of dots appeared within a virtual square region approximately 11° on a side.

The participants' task was to indicate which of the two intervals contained a biological motion sequence, guessing if necessary. Auditory feedback was provided following each incorrect response. The number of noise dots presented on a given trial was determined by the participant's performance on the previous trial(s), according to a

two-up/one-down staircase procedure that converges onto the noise level producing approximately 71% correct detection probability. The staircase was terminated after 16 reversals in the direction of the staircase, and the threshold was estimated as the average number of noise dots over the last six reversals of the staircase.

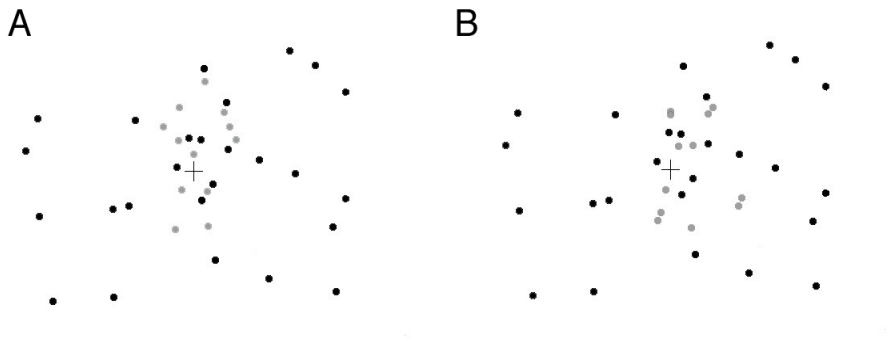

Figure 8. The biological motion detection task. The two intervals are presented in turns, separated by 0.5 s blank screen. A: Biological motion interval. Gray dots indicate biological motion. B: Scrambled motion (gray dots) interval. In actual experiment, all dots were colored black. Noise dots had the same local motion trajectories as that of biological motion or scrambled motion for efficient masking.

"*Reading the Mind in the Eyes" Task (Eyes Task):* For all participants, the ability of Theory of Mind (ToM), which is an important aspect of social functioning, was assessed with the revised version of the "*Reading the Mind in the Eyes*" Task, or the "*Eyes Task*" for short (Baron-Cohen et al., 2001). Participants' general social functioning was assessed using the Zigler social competence scale (Zigler & Levine, 1981) like in experiment 1. However, the Zigler scores provide only a very crude estimate of social functioning because of its broad categorization of variables and dependence upon self-report, whereas the Eyes Task provides a more precise estimate of social functioning based on one's observable performance. For these reasons, the Eyes Task was

additionally used to estimate participants' social functioning. The task involves looking at photographs of the eye region of faces, and making a forced choice among which of four words best describes what the person (in the photograph) might be thinking or feeling (Fig. 9). Therefore, the Eyes Task involves theory of mind skills in the sense that the observer has to understand and interpret mental state that matches the face (eye region). The Eyes task has been well validated as an adult test of theory of mind (Baron-Cohen et al., 2001), which is good for the participants in this study because many previous tests of ToM applied in schizophrenia research have been adopted from psychological tasks developed to test young children's ability to infer others' mental states (e.g. Doody, Götz, Johnstone, Frith, & Owens, 1998). The Eyes task, thus, has more usefulness in the sense that participants' social functioning as an adult is actually assessed. However, it also has its limit in terms of assessing a specific aspect of social functioning rather than a general ability. The number of trials (photographs) was 36. Participants were told to respond as quickly as possible even though there was no time limit to respond. The participants could refer to a glossary of terms if they did not understand the meaning of a certain word. All photographs were presented on the TFT-LCD screen with a touch-screen device, and the participants responded by touching a word they chose. The number of correct responses was recorded as an index of a participant's performance. 3 patients and 2 controls did not participate at follow-up. As a result, the Eyes task scores were collected from 10 controls and 12 patients.

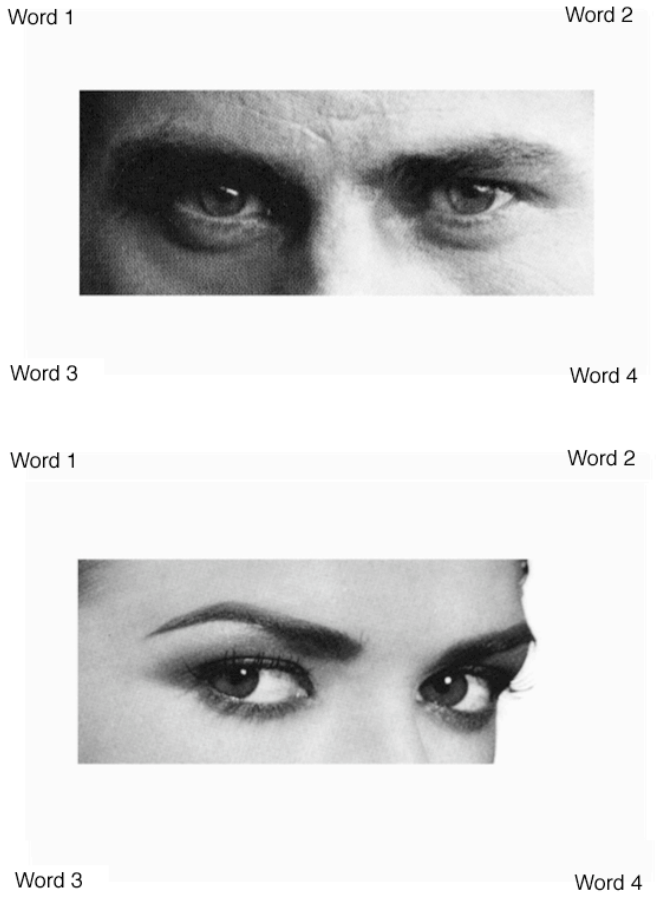

Figure 9. Two example pictures of the "Reading the Mind in the Eyes" task. The testing words expressed possible mood and affect of the faces. (Adapted from Baron-Cohen et al., 2001).

Results

Biological motion detection task Mean (SE) noise levels at which performance was approximately 71% correct (i.e. approximately midway between chance and perfect on this two-alternative forced-choice task) in the schizophrenia group and control group are shown in Fig. 10. Mean (SE) number of noise dots was 40.83 (4.39) in schizophrenia group, and 55.96 (4.36) in healthy control group. This difference was statistically significant ($t(26) = 2.43$, $p < 0.03$). Therefore, this result indicates that patients with schizophrenia had difficulty detecting biological motion within noise dots compared to

healthy controls, in addition to having a poorer ability to discriminate biological motion found in experiment 1.

Reaction times were not recorded on a trial-by-trial basis. The total elapsed time for each test session was measured to find if any other confounding factors, such as poor attention or abnormally shortened (or lengthened) decision-making process in patients, affected performance. There was no significant difference between the groups on this measure ($t(26) = 1.22$, $p = 0.23$). Therefore, it is unlikely that the patients' overall poorer performance arose from these confounding variables.

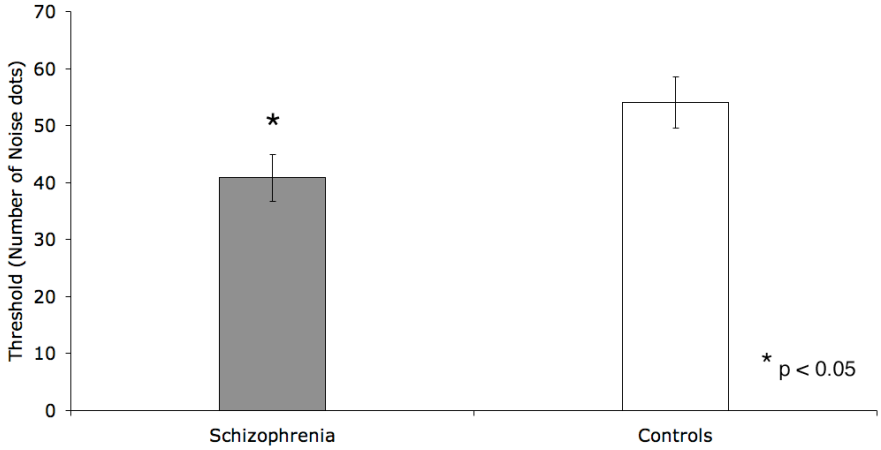

Figure 10. Mean thresholds (the number of noise dots) in the two groups. Error bar indicates 1 standard error of means (SE)

Correlation with symptom severity Correlations between performance on the task (threshold of the number of noise dots) and symptom severity (BPRS for overall, SAPS for positive symptoms, and SANS for negative symptoms) were investigated for the schizophrenia group. No significant correlation with symptom severity was observed (BPRS: $r = 0.17$, $p = 0.57$, SAPS: $r = 0.16$, $p = 0.58$, SANS: $r = -0.14$, $p = 0.63$,

respectively). Furthermore, other demographic variables (age, education level, IQ, and illness duration) were not correlated with performance on the task.

Social functioning and correlation with detection of biological motion Consistent with the results from experiment 1, group difference in Zigler scale was statistically significant. Patients also recorded significantly lower scores in the Eyes task, compared to healthy controls, as shown in Table 2. Therefore, these results indicate that schizophrenia patients are generally impaired in their social functioning.

For all participants, Zigler scores were correlated with the Eyes task scores, and the correlation was statistically significant ($r = 0.47$, $p < 0.03$, Fig. 11A). Within each group, the correlations were not significant (schizophrenia: $r = -0.01$, $p = 0.98$, controls: $r = 0.27$, $p = 0.43$). Correlation between performance on the biological motion task and Zigler score (Fig. 11B) reached significance ($r = 0.44$, $p < 0.02$), which is similar to results from Experiment 1 (see Fig. 7). Performance on the biological motion task and the Eyes task, on the other hand, did not significantly correlate ($r = 0.21$, $p = 0.34$).

To summarize, the participants with schizophrenia had impaired social functioning compared to healthy controls as indicated by significant group difference on both the Zigler scale and the Eyes Task, and there was a tendency for these indices of social functioning to correlate with participants' ability to detect biological motion.

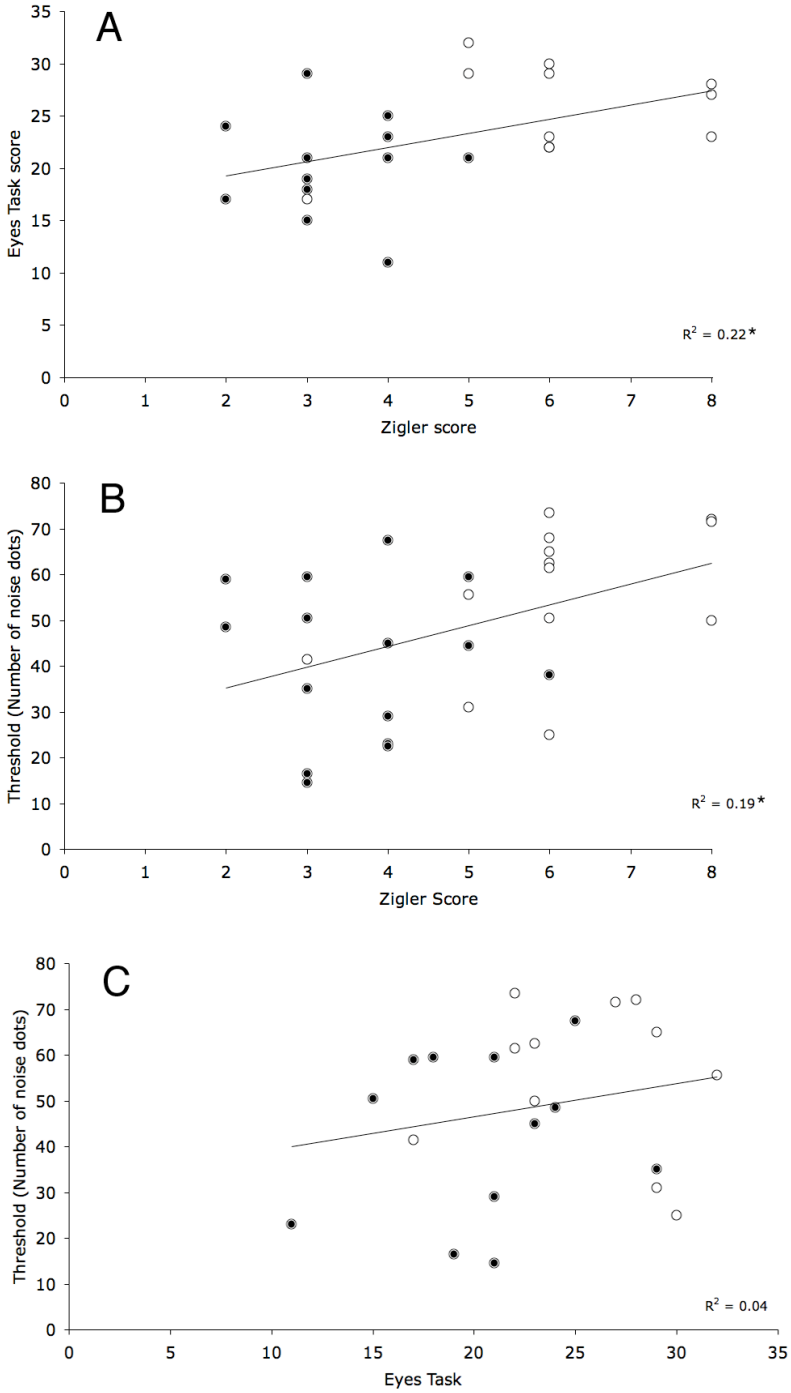

Figure 11. Correlations. Filled dots indicate the patients with schizophrenia. A: correlation between the Zigler score and the Eyes Task score. B: Correlation between the Zigler score task and performance on the biological motion task. C: Correlation between the Eyes task and performance. * $p < 0.05$

Discussion

In experiment 2, biological motion signals were superimposed on a variable number of distracting noise dots. Results revealed that patients with schizophrenia had a deficit in detecting biological motion when compared to performance by controls. In addition, they had a deficit in distinguishing biological motion from scrambled motion (experiment 1). On the bases of these results, it is possible to argue that the deficits in biological motion perception in schizophrenia is robust regardless of specific aspects of perceptual demands, i.e. discrimination versus detection.

As mentioned earlier, patients with schizophrenia have difficulty perceiving coherent, translational motion within randomly moving noise dots (e.g. Chen et al., 2003b). Therefore it is necessary to discuss an alternative interpretation based on the reported deficit in general motion perception and similar 'first-look-appearances' between the task stimuli used in this study and the widely used RDC in motion perception studies. That is, one could argue that both the biological motion and RDCs require integration of spatially distributed local features appearing amongst distracting elements, and biological motion animations represent a particularly complex class of visual stimuli, embodying hierarchical, pendular motions that are much more difficult to perceive than the simpler, translational motion signals defining RDC. Therefore, poor detection of biological motion might be merely an extension of impaired global motion processing in schizophrenia. However, converging lines of evidence indicate that perception of biological motion is remarkably efficient and can be accomplished with very brief exposure durations and in the presence of massive levels of random motion masking noise (Blake and Shiffrar, 2007). Indeed, PL animations are highly perceptually

salient and "complex" only in that the motion vectors defining those animations portray kinematics and not just rigid transformations.

In addition to the issue of uniqueness of biological motion, there is more evidence to indicate the dissociation of processing of RDC and PL animations. Studies of coherent motion (i.e. RDC) detection suggest two elementary processes; one for rejecting the noise component embedded in the stimulus in an early stage of motion perception process and the other for integrating signal components in the late stage of the motion processing (Chen et al., 2005; Watt & Phillips, 2000). In fact, area MT and the medial superior temporal (MST) area have a modular organization suitable for these processes: the lateral area of MT representing the fovea has small receptive fields (Dursteler & Wurtz, 1988; Dursteler, Wurtz, & Newsome, 1987; Newsome & Pare, 1988; Newsome, Wurtz, & Komatsu, 1988), a lateral area of MST (MSTl) has a mixture of small and large receptive fields (Dukelow et al., 2001), and the dorsal MST (MSTd) is known as having large receptive fields (Duffy & Wurtz, 1991; Saito et al., 1986).

On the other hand, there is evidence suggesting that the perception of biological motion depends on top-down, holistic processing (Bertenthal & Pinto, 1994; Bülthoff, Bülthoff , & Sinba, 1998; Cavanagh, 1992, 1999; Dittrich, 1993) in addition to bottom-up, local processing (Johansson, 1973; Mather, Radford, & West, 1992). For example, Bertenthal and Pinto (1994) used a dual task in which participants were told to detect biological motion while detecting orientation change of rectangles on the same display. One of the two types of displays had biological motions surrounded by randomly moving dots, and the other had biological motions with a "scrambled mask" that mimicked the motion of each dot forming the biological motion. Their results showed that a

participant's performance was strongly hampered in the dual task with "scrambled mask" condition, suggesting that top-down, holistic processing was required. In fact, the displays used in the current experiment are quite similar to those used by Bertenthal and Pinto (1994); the elements of "noise (mask)" in my experiment also consisted of the dots forming the biological motion within the same display. Therefore, the detection deficits of the patients found in the current experiment may have been caused by inefficient top-down processing rather than impaired sensory, bottom-up processing.

However, it is still possible that biological motion perception could be disturbed by an impaired bottom-up process or dysfunction within the earlier motion area MT. The limitation of the current experiment is the lack of the global motion data from the same participants. This possibility is tested in the experiment in CHAPTER IV, a functional magnetic resonance imaging study in which both MT and STSp activation in response to biological and non-biological motion is compared.

As for the relationship between biological motion perception and social functioning, the results are consistent with that of experiment 1, as indicated by a significant group difference in the Zigler score and the Eyes task score, and the association between performance on the biological motion detection task performance and social functioning across all participants (Fig. 11B & C). Furthermore, a significant correlation was observed between the two social functioning tests, the Zigler score for general social functioning and the Eyes task for ToM (Fig. 11A). This result suggests that the participants' social functioning was reliably measured and that deficient biological motion perception might contribute to impaired social functioning, or at least is concurrent with reduced social functioning.

To summarize, experiment 2 revealed another aspect (detection) of impaired biological motion perception in schizophrenia, which does not seem to be a mere extension of impaired motion perception. It also seems that efficiency of social functioning is associated with enhanced biological motion perception. In the following experiment, a more detailed exploration of the nature of the deficit in biological motion perception was investigated using a series of parametrically scrambled biological motion stimuli.

Experiment 3: Perception of biological motion signals from parametrically scrambled biological motion

In experiments 1 and 2, schizophrenia patients showed deficits in dissociating biological motion and scrambled motion regardless of task demands. Experiment 3 aimed to further investigate the characteristics of the observed deficits. Specifically, experiment 3 employed a series of parametrically scrambled PL animations with a 15% spatial scrambling step, and participants were asked to discriminate two differently scrambled biological motion sequences by indicating which one was closer to the original biological motion. Specifically, the four conditions of discrimination consisted of discriminating 0% (biological motion) vs. 15%, 15% vs. 30%, 30% vs. 45%, and 45% vs. 60% scrambled motions. By doing this, it is possible to observe the extent to which one's ability to discriminate biological motion from non-biological motion varies with increasing amount of scrambling. In other words, this experiment is designed to test group differences in biological motion perception according to the amount of available spatial information embedded in the biological motion sequence. This experiment also aims to determine the critical "amount" of biological features that clearly dissociate performance of patients

with schizophrenia from that of healthy controls. It was hypothesized that patients with schizophrenia would show weaker discrimination within each of the scrambling conditions in general, considering their lower sensitivity of discrimination (*d′* values) observed in experiment 1. Furthermore, patients would require less scrambled motions for comparable performance to that of normal controls when considering patients' poor detection of biological motion in experiment 2.

Methods

Participants

Seventeen outpatients (7 females and 10 males) who met the criteria for schizophrenia and schizoaffective disorder in the DSM-IV (American Psychiatric Association, 1994) participated in the experiment. During the participants' initial interview, they were screened by the exclusion criteria including current substance use, brain injury, any neurological disorder, and mental retardation. Diagnosis was determined on the basis of the SCID (Spitzer & Williams, 1985). Symptom severity was assessed with BPRS for overall symptoms (Overall & Gorham, 1962), SAPS for positive symptoms and SANS for negative symptoms (Andreasen & Olsen, 1982). Mean BPRS score was 15.06 (SD = 9.88). Mean SAPS and SANS scores were 14.93 (SD = 11.13) and 21.13 (SD = 15.88), respectively. Mean age was 39.6 (SD = 9.3) and education level was 14.4 (SD = 1.7) years. Their mean IQ, assessed with the Wechsler Abbreviated Scale of Intelligence (WASI ^{TM}), was 101.76 (SD = 22.65). Sixteen healthy controls (8 females and 8 males) were recruited from the local community through advertisement. Healthy participants were excluded if they had any DSM-IV Axis I disorder, or a family history of

psychotic illness. Mean SPQ score of the healthy controls was 13.31 (SD = 7.19). Controls' mean age, education level, and IQ were 36.2 (SD = 2.16) years, 15.6 (SD = 2.16) years, and 103.8 (SD = 12.9), respectively. Patients with schizophrenia and healthy controls were not significantly different in age ($t(31) = 1.25$, $p = 0.22$), education ($t(31) = 1.59$, $p = 0.12$), and IQ ($t(31) = 0.31$, $p = 0.76$). For all participants, their general social functioning was estimated on the basis of the Zigler social competence scale (Zigler & Levine, 1981), and their ability of ToM was assessed with the revised version of the Eyes Task (Baron-Cohen et al., 2001). Unfortunately, 4 out of 17 patients and 3 out of 16 controls could not be assessed on the Eyes task because they were lost at follow-up. A significant group difference was observed on both social scales (Zigler scale: $t(31) = 6.24$, $p < 0.001$; Eyes Task: $t(24) = 2.11$, $p < 0.05$), consistent with results in the previous two experiments.

Table 3. The demographic data

	Control subjects (n = 16)	Schizophrenic subjects (n = 17)	*p*
Age	35.6 (2.47) [A]	39.6 (9.3)	n.s.
Education (years)	15.5 (2.23)	14.4 (1.7)	n.s.
WASI IQ Score	103.8 (12.9)	101.8 (22.7)	n.s.
BPRS	n/a [B]	15.1 (9.8)	
SAPS	n/a	14.9 (11.1)	
SANS	n/a	21.1 (15.9)	
SPQ	13.3 (7.2)	n/a	
Handedness (L/R/Ambi)	2/14/0	0 /16 / 1	
Illness duration (years)	n/a	15.1 (8.5)	
Zigler score	6.19 (1.27)	3.65 (1.06)	< .001***
Eyes task [C]	25.00 (4.81)	20.92 (5.06)	< .05*

[A] Mean (standard deviation)
[B] Not applicable
[C] Revised version of the Reading the Mind in the Eyes Task (Baron-Cohen et al., 2001). 14 controls and 13 patients were tested on the Eyes task.

Apparatus

The task was presented on a CRT monitor (120Hz, 21 inches, TOTOKU Calix) connected to a Macintosh computer (Power Mac G5) and controlled by Matlab © (Mathworks Inc. Natick, MA) and the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). The experiment was conducted in a dimly lit room where the only light source was the computer screen. The viewing distance was 64 cm.

Stimuli: The same series of PL animations in the experiment 1 and 2 was used again to present biological motion depicting familiar human activities; 10 different types of motion were used. From each of the biological motion stimuli, 4 different spatially scrambled animations (15%, 30%, 45%, and 60%) were created in the following way. Initially, the starting frame of a biological motion sequence was taken (as shown by black dots in Fig. 12), and 100% scrambled animation was created by spatially randomizing the initial position of each dot. Next, intermediate locations were generated between the biological sequence and its corresponding 100% spatially scrambled sequence to create a series of parametrically scrambled animations. For example, dot A is one of the dots forming biological figure and moves into the position of the A′ when the motion is scrambled. Position (a) represents an intermediate position that divides the distance between A and A′ with the ratio of 15:85. Therefore, 15% spatially scrambled motion can be created when 15% of intermediate positions for all the other dots are taken. In the same way, 30%, 45%, and 60% scrambled motion sequences were created from 10 different biological motion sequences. Therefore, 1 set of stimuli had 50 different animations (10 different motion sequences × 5 conditions of scrambling (0~60%)). Three

more sets of scrambled stimuli were also created to avoid the possibility that identical animations were presented to the participant repeatedly. For example, four 15% scrambled motions in each set had similar configuration but were never identical because the completely scrambled motions in each set were always different. During the experiment, the same number of motion sequences was selected from each set of stimuli.

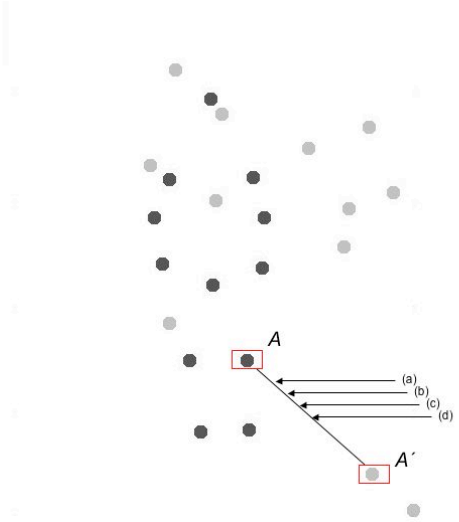

Figure 12. Creation of a series of partially scrambled animations. Black dots indicate the dots forming a biological motion and gray dots form a spatially scrambled motion by randomizing initial positions of each dot. Dot A´ indicates a new location of dot A when the motion is 100% spatially scrambled. (a) is an intermediate position that divides the distance between A and A´ into 15:85. Therefore, when the position '(a)'s are taken from all pairs of biological – scrambled dots, spatially 15% scrambled motion sequence is generated. In the same way, (b),(c), and (d) represent the dot positions of 30%, 45%, and 60% scrambled motion.

The biological motion task: Discrimination of two differently scrambled motions

This task used a two-alternative, spatial forced-choice procedure to assess the ability to discriminate between two differently scrambled animations. In each trial, two motion sequences were presented side-by-side, left and right of the center of the screen simultaneously, lasting 1 s. The participant's task was to indicate which motion sequence

(left or right) looked closer to human activity by pressing one of the pre-assigned keys, guessing if necessary. This task was similar to the task used in experiment 1, except that two motion sequences were displayed instead of just one. Two motions were displayed because there was no correct answer to the series of partially scrambled sequences if they were shown alone. But by comparing two differently scrambled sequences, a correct answer always exists in every trial so that participant's ability for fine discrimination can be precisely measured. Pairing of two partially scrambled motion sequences was not random. But rather, the paired sequences always had a 15% scrambling difference. Therefore, there were 4 different conditions of stimuli presentation: 1) 0% (biological) vs. 15%, 2) 15% vs. 30%, 3) 30% vs. 45%, and 4) 45% vs. 60% scrambled motion sequences. The order of those 4 motion pairs and the types of original biological motions were randomized over trials. The total number of trials was 160 (10 original biological motion $\times$ 4 motion pairs $\times$ 4 sets of stimuli). The two motion sequences in each trial fell within a rectangular region subtending approximately 9° (width) and 6° (height). Visual angle from the fixation point to the closest point of motion sequences on the left or right was approximately 2.7°. During the presentation of the stimuli, the participant could move his/her eyes back and forth to observe the two motion sequences. There was no time limit for a response and no visual or auditory feedback was given subsequently. Before the actual testing, a few biological, partially scrambled and scrambled motion sequences were shown as examples, and practice trials were also given to each participant.

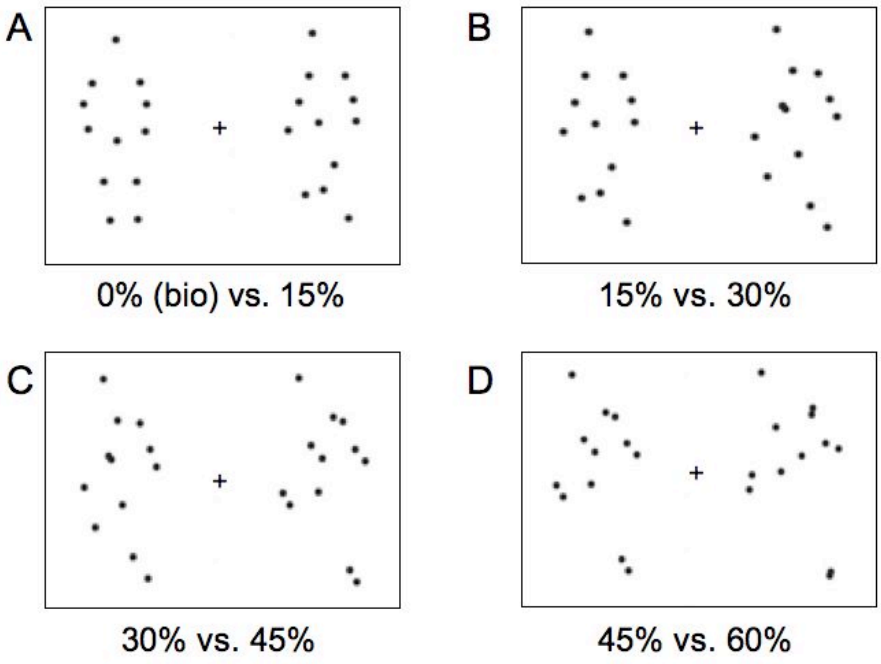

Figure 13. Examples of the four discrimination conditions. Over the trials, these pairs of differently scrambled animations were presented in random order, and the participants were asked to indicate which one (left or right) is closer to original human motion. % below each figure means the percent of spatial scrambling.

Results

Partially scrambled biological motion discrimination task Descriptive statistics of mean (SE) accuracy in each condition and overall are shown in Table 4. Multifactorial repeated measures ANOVA revealed a significant main effect of diagnosis (group) ($F(1,31) = 28.99$, $p < 0.001$). Patients with schizophrenia were less accurate in discriminating two differently scrambled motions than healthy controls. This finding was consistent with the results from experiment 1. A main effect of the scrambling conditions was also observed ($F(3,93) = 99.93$, $p < 0.001$), indicating that the participants had difficulty, as expected, discriminating two differently scrambled motions as they increased in extent of spatial scrambling.

Table 4. Descriptive statistics of performance on the task

	0% vs. 15%	15% vs. 30%	30% vs. 45%	45% vs. 60%	Overall
Schizophrenia (N = 17)	75.44 (2.08)[a]	69.12 (2.29)	51.88 (2.10)	51.88 (2.14)	62.08 (1.32)
Controls (N = 16)	89.06 (2.14)	82.19 (2.36)	65.47 (2.17)	52.50 (2.21)	72.30 (1.36)

[a] Mean accuracy (%) and standard error of the means

In addition to the main effects, a significant interaction between diagnosis and the conditions of scrambling (stimuli pairs) ($F(3,93) = 5.17$, $p < 0.01$) was found. Healthy controls showed an approximately linear decrease of discrimination accuracy with increased scrambling and reached chance accuracy at the condition of discrimination between 45% and 60% scrambled animations. Patients with schizophrenia also showed an accuracy decrease with increased scrambling. However, they reached chance accuracy when the stimuli pairs of 30% and 45% scrambled animations were presented. They further showed chance accuracy at the condition of 45% vs. 60% scrambling. In summary, patients with schizophrenia had poorer ability of discrimination between two differently scrambled motions in general (main effect). Furthermore, they reached chance accuracy earlier, which indicates that patients require larger amounts of biological features of motion signals for successful discrimination (interaction effect).

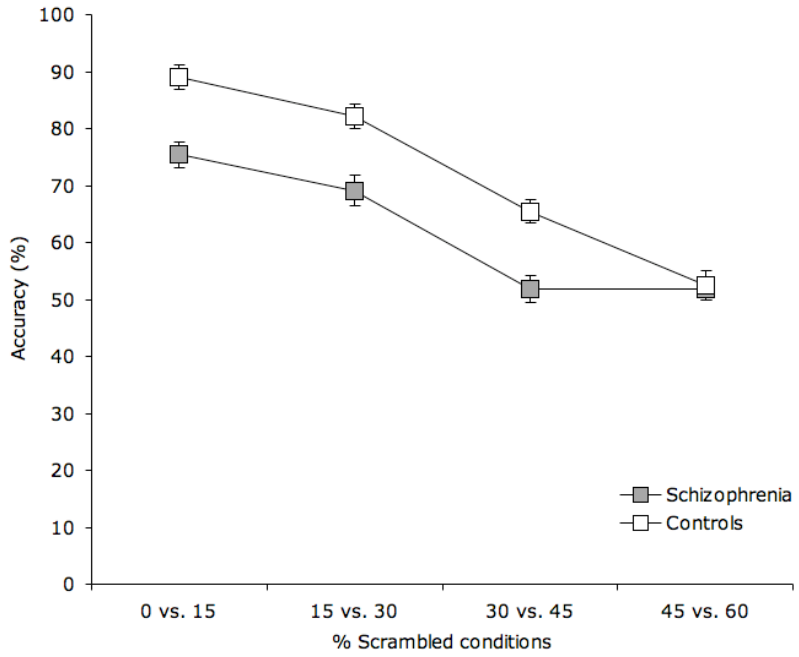

Figure 14. Performance (accuracy of discrimination) on the task in the schizophrenia group and healthy control group. Error bars indicate one standard error of means (SE).

Correlation with symptom severity For patients with schizophrenia, correlations between symptom severity (BPRS, SAPS, and SANS scores) and their performance on the task (accuracy in each scrambling condition and overall accuracy) were examined. No significant correlation was found (BPRS: $r = 0.05$, $p = 0.85$, SAPS: $r = -0.13$, $p = 0.96$, SANS: $r = 0.25$, $p = 0.34$, correlation with overall accuracy). Other demographic variables, including age ($r = 0.34$, $p = 0.17$), education level ($r = 0.23$, $p = 0.38$), IQ ($r = 0.15$, $p = 0.57$), and illness duration ($r = 0.198$, $p = 0.46$) were not correlated with performance on the task.

Correlation with social functioning As in the previous experiments, Zigler social competence scale (Zigler & Levine, 1981) for estimating general social functioning and the Eyes Task (Baron-Cohen et al., 2001) for assessing the ability of ToM were used to

estimate social functioning. As described in Table 3., the patients with schizophrenia in this experiment showed a significantly lower score on both the Zigler scale ($t(31) = 6.24$, $p < 0.001$) and the Eyes task ($t(24) = 2.11$, $p < 0.05$), compared to healthy controls. For all participants[1], the Zigler scores and the Eyes task scores were significantly correlated ($r = 0.41$, $p < 0.05$, Fig. 15A), although the correlations did not reach significance within each group ($r = 0.08$, $p = 0.79$ in schizophrenia, $r = 0.26$, $p = 0.39$ in controls). Correlations between the Zigler score and overall accuracy, and between the Eyes task score and overall accuracy are shown in Fig 15B and C, respectively. These correlations were statistically significant (Zigler score: $r = 0.54$, $p < 0.005$, Eyes Task: $r = 0.47$, $p < 0.02$). On correlations with individual conditions of scrambling, the Zigler score was positively correlated with 3 out of 4 scrambling conditions, except for the condition of 45% vs. 60% scrambling on which all participants recorded chance accuracy. The Eyes task was positively correlated with 2 out of 4 scrambling conditions (15% vs. 30% and 30% vs. 45% scrambling conditions). Within each group, those correlations did not manifest strongly. In the schizophrenia group, the Eyes task was correlated with one condition (15% vs. 30% scrambling, $r = 0.72$, $p < 0.01$) and overall ($r = 0.59$, $p < 0.05$), and the Zigler score did not correlate with performance on any condition. In the healthy control group, the Zigler score was correlated with accuracy on 30% vs. 45% condition ($r = 0.51$, $p < 0.05$).

[1] Note that the Eyes task data were collected from 13 patients and 13 controls only (see Methods). So the correlation analyses are restricted to this population.

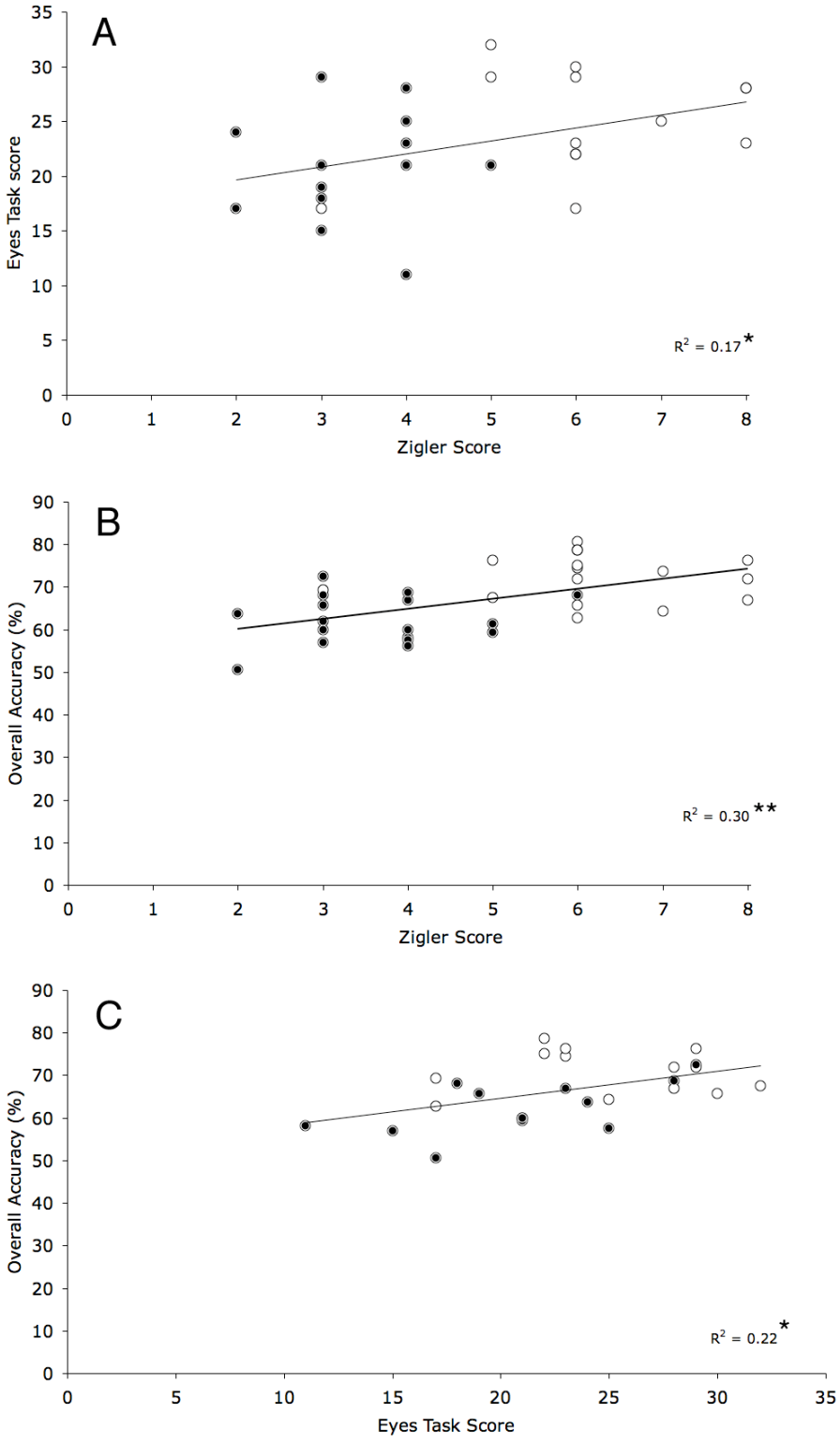

Figure 15. Correlation among the Zigler scale, the Eyes Task, and Overall accuracy of discriminating partially scrambled motion sequences. Filled symbols indicate the data from schizophrenic patients. Top: correlation between Zigler score and Eyes task. Middle: Correlation between Zigler score and overall accuracy. Bottom: Correlation between Eyes task score and Overall accuracy. * $p < 0.05$, ** $p < 0.01$

Discussion

Consistent with the results from the two previous studies, patients with schizophrenia performed worse on the task of discrimination between two differently scrambled motions than normal controls. On three conditions of discrimination – 0 vs. 15%, 15 vs. 30%, and 30 vs. 45% scrambled motions – patients showed statistically significant lower accuracy in selecting the sequence that looked more human motion. When the two motion sequences were spatially scrambled with approximately 50% scrambling (i.e. when the characteristics of biological motion almost disappeared in the two motions), both the patients and controls were at chance accuracy.

The results from the control group indicated that the extent of successful perception of biological motion decreases with increased spatial scrambling of motion. Furthermore, an approximately linear decrease of discrimination accuracy in the control group suggests that the spatial scrambling method in the present experiment reliably controlled the 'amount' of biological features in the PL animations quantitatively. The linear decrease of behavioral accuracy observed in healthy controls in the present experiment may reflect modulated activation in STS according to the available amount of biological information embedded in the stimuli. Indeed, there exists physiological evidence that activity within STSp is modulated by the amount of biological features and how well they are organized. For example, STSp in the right hemisphere is strongly activated by motion of a human figure and the motion of a human-like robot, but not strongly activated by nonmeaningful mechanical motion(i.e. a scrambled robot motion, consisting of the same 'parts') and non-biological pendular motion (Pelphrey et al., 2003). STSp is also activated by inverted PL biological motion, but this activation is not as strong as upright ones (Grossman &

Blake, 2001).

On the other hand, patients' lower accuracy on the task in this study indicates that their ability to process biological motion signals embedded in partially scrambled motion was significantly impaired. This finding is consistent with the previous experiments. The task in this study required a more refined ability of detection in addition to discrimination in order to successfully select more 'human-looking' motion: The participant had to judge whether the two presented animations were biological, and also had to detect the difference of 15% scrambling between the two motion sequences. Therefore, the patients' lower accuracy across the scrambling conditions (except the 45 vs. 60% scrambling condition) suggests that they may have difficulty discriminating biological motion from scrambled motion (like in the experiment 1). Furthermore, their ability to detect a organized hierarchical, pendular motion characterizing biological motion through the comparison of two scrambled motion may also be impaired (similar to the experiment 2).

The most interesting result was obtained from the condition of 30 vs. 45% scrambling. In this condition, normal controls showed significantly higher accuracy (65.5%) than chance level while patients with schizophrenia remained at chance accuracy (51.9%). This finding suggests that the spatial scrambling range of 30% ~ 45% may be a critical range that determines chance performance in perceiving biological motion in patients with schizophrenia, whereas controls seem to have this point around 50% scrambling. As mentioned above, modulation of STSp activation may be dependent upon the amount of biological characteristics within the motion. Therefore, on the basis of the results from the present experiment, it is reasonable to predict that the patients' STSp activation to biological and scrambled motion will be different from those of controls. In

addition, it will be also interesting to observe activation within STSp to partially scrambled motions that are spatially scrambled between 30% and 45% in schizophrenia and controls. All of these hypotheses are tested in experiment 4, CHAPTER IV.

It is necessary to speculate a possible mechanism that could account for patients' poorer discrimination between two scrambled motion with a 15% difference in scrambling. One possibility is that patients may have failed to process the characteristics of biological motion (hierarchical, pendular motion) appropriately. That is, they may simply have a deficit in processing biological motion signals. Another possibility is that patients have a tendency to process (partially) scrambled motion as biological motion. Considering the results from experiment 1 with these current results, the latter is more plausible to account for the current results. Note that patients showed a higher false-alarm rate in a simple discrimination task in experiment 1. That is, patients' lower accuracy of discrimination in the condition of 30% vs. 45% scrambling does not mean they have failed to process biological features in the 30% scrambled motion, but their tendency of processing 45% scrambled motion like 30% scrambled motion might have biased their discrimination.

In more general terms, therefore, patients with schizophrenia may have difficulty filtering or attenuating inappropriate visual stimuli. In fact, in the temporal domain of early sensory processing, it is known that the patients show the phenomenon of sensory gating deficits, which means they usually fail to normally filter or attenuate the second of two stimuli that are closely linked in time (Braff, Grillon, & Geyer, 1992; Green et al., 1994b). For example, in the startle-blink paradigm (Braff et al., 1992) in which the electromyogram amplitude is measured to a blink-eliciting stimulus (e.g. a loud noise),

the amplitude of the blink is usually reduced if the blink-eliciting stimulus is preceded by another stimulus. However, patients with schizophrenia often fail to attenuate the response to the second stimulus. Similarly, patients with schizophrenia require significantly longer time to escape from the visual backward masking (VBM) effect, probably because of a failure to attenuate the disruptive effects of the mask (Green et al., 1994b). In cognitive functions, it is also widely known that patients with schizophrenia show impaired cognitive inhibition, a neuropsychological concept that refers to resolving cognitive conflict and ignoring irrelevant information (Aron, Robbins, & Poldrack, 2004; Barch et al., 2001; Bradshaw, 2001; Bunge, Ochsner, Desmond, Glover, & Gabrieli, 2001; Wright, McMullin, Martis, Fischer, & Rauch, 2005), as indicated by reduced negative priming and increased Stroop interference (Barch et al., 2001; MacDonald, Cohen, Stenger, & Carter, 2000; Steel et al., 2001). Therefore, the phenomena of "failure of attenuation" or inefficient filtering of irrelevant stimuli are widely spread impairments that extend from the sensory stage to higher levels of cognitive functioning in schizophrenia, and it is possible to interpret the current results in a similar vein. Finding the neural correlates of impaired discrimination of partially scrambled motion in schizophrenia could elucidate this speculation. That is, patients with schizophrenia may show a smaller difference between activation to biological motion and to scrambled motion, or their STSp activation to scrambled motion could be greater, compared to that of normal controls.

One may ask if patients' tendency to 'false-alarm' could be raised by their positive symptoms, especially by visual hallucinations. This is another possible alternative, however, I did not find any significant correlation between positive symptom scores and

false alarm rate (experiment 1) or accuracy of discrimination in this experiment. Moreover, most of the participants with schizophrenia tested had more severe negative symptoms than positive symptoms in general. This hypothesis could be tested more precisely with patients who have severe positive symptoms. But it is unlikely that the deficit in biological motion perception is associated with symptoms of schizophrenia according to the results from experiments described in this chapter.

The correlations between performance on the biological motion task and general social functioning (Zigler scores) or Theory of Mind (Eyes task scores) were similar to those in the previous two experiments. There was a significant group difference in both social functioning scores, and the Eyes task score and Zigler scores were significantly correlated. In addition, the significant correlation between social functioning and overall accuracy of discrimination suggested that people with higher social functioning tended to perform better on the biological motion discrimination task. However, like in the previous experiments, the correlations were not significant within each group, although it seems that the Eyes task score has some positive relation with performance on the biological motion task, as shown in Fig. 15C. Taken together, it is consistently shown that better perception of biological motion may be coupled with higher social functioning in the general population, but it does not necessarily reflect the severity of impaired social functioning.

General Discussion

In CHAPTER III, biological motion perception in schizophrenia was investigated with three different behavioral experiments. Experiment 1 found, for the first time, that

patients' ability to discriminate between biological and scrambled motion is impaired compared to healthy controls. In addition to the lower sensitivity to discriminate biological motion, schizophrenia patients also exhibited poorer detection when the biological motion signals were embedded in distracting noise elements that had the same local motion trajectories as the dots forming biological motion (experiment 2). In experiment 3, further details of the observed deficit in experiment 1 and 2 were investigated with a task that required fine discrimination between biological sequences partially scrambled at different magnitudes. Both patients with schizophrenia and healthy controls showed decreasing accuracy of discrimination with increased spatial scrambling, but schizophrenia patients showed lower accuracy than controls in general. This finding was consistent with the result from experiment 1. In addition, schizophrenia patients reached chance accuracy when the two scrambled motions were between 30% and 45%, while healthy controls performed at a significantly higher accuracy in the same condition.

The results from these three behavioral experiments indicate that patients with schizophrenia have difficulty perceiving biological motion signals regardless of task demands. Impaired biological motion perception appears to be more than a simple extension of visual deficits that originate from early stages of visual processing, such as primary visual cortex. This is indicated by the patients' comparable performance on the global form task to that of healthy controls in experiment 1. Moreover, observed deficits in biological motion perception in schizophrenia are not likely to be caused by patients' difficulty in processing global, coherent motion signals. Rather, previous case studies of brain damage and psychophysical studies have strongly suggested dissociated processing of biological motion and coherent, translational motion (Shenk & Zihl, 1997a,b; Vaina et

al., 1990), and the role of top-down processing in biological motion perception (e.g. Bertenthal & Pinto, 1994).

This interpretation is further supported by the interesting finding on the nature of the deficit in experiment 1. That is, patients' lower discrimination sensitivity was based on their strong tendency to perceive non-biological motion as biological motion (i.e. high false alarm rate). This result also suggests that poor detection and discrimination observed in experiment 2 and 3 could be caused by misattribution of non-biological information to biological signals rather than a failure to process biological motion signals, implicating the role of top-down processing. However, the limitation of this study is that global motion perception was not tested in the same group of patients who participated in the series of biological motion tasks, yet impaired global motion perception has been a consistent finding in several previous studies (Chen et al., 2003; Kelemen et al., 2005; Kim, Wylie, Pasternak, Butler, & Javitt, 2006; Li, 2002; Stuve et al., 1997).

In regards to social functioning, in schizophrenia, patients showed significantly lower scores on both the Zigler social competence scale and the Eyes task, which implicate general social functioning and ToM are impaired. These results are well supported by previous studies that directly address social functioning and schizophrenia (Brüne, 2003; Corcoran et al., 1995; Doody et al., 1998; ; Frith & Corcoran, 1996; Green, Waldron, Simpson, & Coltheart, 2007; Pickup & Frith, 2001; Pilowsky, Yirmiya, Arbelle, & Mozes, 2000; Uhlhaas, Phillips, Schenkel, & Silverstein, 2006). More importantly, both the Zigler scores and the Eyes task scores were significantly correlated with performance on biological motion tasks in experiment 1 and 3, and there was also a weak correlation in experiment 2 for all participants. This finding suggests that impaired

perception of biological motion could co-occur with one's degraded social functioning. However, this interpretation is still limited because significant correlations within each group were not consistently observed. For example, normal controls showed a clear relationship between *d'* and Zigler scores, but the patients did not. This may have been caused by a narrow range of scores in the patient group. Further studies are necessary to understand the relationship clearly.

Taken together, consistent findings of impaired biological motion perception in schizophrenia, and its seemingly co-occurrence with decreased social functioning strongly suggest altered activation within the brain regions involved in both the biological motion perception and social functioning (ToM). Based on past studies, healthy individuals show much stronger activation within the posterior STS (STSp) to biological motion sequences than to scrambled motion sequences. However, considering their strong tendency of perceiving scrambled motion as biological motion, schizophrenia patients are expected to show a relatively smaller activation difference in viewing biological and scrambled motion sequences. This hypothesis is tested in the functional imaging study in the next chapter. In addition, it would also be interesting to see how putative top-down processing in biological motion perception could be reflected in neural activation within the STSp region.

Another issue to be confirmed in the imaging study is, as mentioned above, whether activations within area MT are modulated by presentations of biological or scrambled motion. Previous studies indicated that this is unlikely: MT was equally activated by biological motion and non-biological motion (Grossman et al., 2000; Howard et al., 1996) in healthy individuals. However, schizophrenia patients do have impaired non-

biological motion perception, which implicates their MT function is also compromised. Therefore, it is necessary to test the possible existence of MT dysfunction and how it may affect STSp activation to biological motion in people with schizophrenia.

CHAPTER IV.

NEURAL CORRELATES OF BIOLOGICAL MOTION PERCEPTION IN SCHIZOPHRENIA

The role of the STS region in perception of biological motion has been firmly established in healthy adults (Bonda et al., 1996; Grossman et al.,2000; Howard et al., 1996; Pelphrey et al., 2003; Puce et al.,1998; Vaina, Solomon, Chowdhury, Sinba, & Beliveau, 2001). STS region includes cortex within the STS, adjacent cortex on the surface of the superior and middle temporal gyri, and adjacent cortex on the surface of the angular gyrus (Allison et al., 2000). However, there has been no research on the functional activation to biological motion stimuli within this region in patients with schizophrenia. A past structural imaging study reported partial volumetric reduction in the left superior temporal gyrus in schizophrenia, which may suggest a functional deficit within this area (Shenton et al., 1992). Therefore, the goal of the functional imaging experiment in this chapter was to investigate STS activation associated with the behavioral aberration in biological motion perception in schizophrenia.

Experiment 4. Neural bases of impaired perception of biological motion in schizophrenia: an event-related fMRI study

Experiment 4 investigated the neural correlates of biological motion perception in patients with schizophrenia using an event-related fMRI design. Several previous imaging studies consistently reported that the STS, especially its posterior region, is reliably and selectively responsive to biological motion signals (Grossman et al., 2000; Grossman & Blake, 2001). Furthermore, its activation can be modulated by clarity of the

motion, such as inverted or imagined biological motion (Grossman & Blake, 2001), by extent of meaningfulness (Pelphrey et al., 2003), and by learning (Casile & Giese, 2006; Grossman et al., 2004). Since the deficits in biological motion perception in patients with schizophrenia was newly found in the previous behavioral studies discussed, the next reasonable step is an imaging study to understand how schizophrenia patients utilize their brain while they detect or discriminate biological motion signals successfully.

Behavioral results strongly suggest that schizophrenia patients may show different patterns of activation within the STSp to biological motion tasks. Specifically, patients were less sensitive in distinguishing biological motion from scrambled motion (experiment 1), required fewer number of noise dots to detect biological motion successfully (experiment 2), and were poorer in detecting differences in scrambling between two partially scrambled biological motions (experiment 3). All of these results suggest a possibility of less selective activation to biological motion within STSp of schizophrenia patients. Furthermore, patients' lower sensitivity of discrimination was mainly due to their strong tendency of incorrectly responding "biological motion" to scrambled motion (i.e. "false-alarm"), which allows us to speculate that their STSp may be more strongly activated by scrambled motion compared to normal controls. In the least, it is possible to predict that the activation difference when viewing biological motion and scrambled motion would be smaller in schizophrenia patients than in normal controls.

To clarify these hypotheses, experiment 4 primarily aimed to investigate STSp activation associated with biological motion perception in schizophrenia using an event-related designed discrimination task in which the participants were instructed to judge

whether a given motion was biological or non-biological motion. In the task, a series of biological motion, scrambled motion, and 37% spatially scrambled motion animations were presented. The third category of stimuli, 37% scrambled motion, was employed based on the results from experiment 3, in which schizophrenia patients performed at chance accuracy in discriminating 30% vs. 45% scrambled motion, while normal controls showed significantly higher accuracy. It was assumed this range of scrambling may create the most ambiguous motion that divides the patients' responses. Therefore, because only one motion was presented in the task, the midpoint (37%) was set as the ambiguously scrambled biological motion.

The second purpose of this study also aimed to observe activations within the motion-sensitive area MT to the same stimuli. Since impaired perception of global motion has been reported and area MT was implicated (e.g. Chen et al., 2003b), clarification is needed to determine whether the patients show MT dysfunction to stimuli of the task. Furthermore, clarification is also needed to determine whether possible MT dysfunction would affect STSp activation and biological motion perception in schizophrenia.

Methods

Participants

Nine outpatients with schizophrenia (5 females and 4 males) participated in the experiment. 6 out of nine patients participated in experiment 3. All met the criteria for schizophrenia and schizoaffective disorder in the DSM-IV (American Psychiatric Association, 1994). Clinical symptoms were assessed with the Brief Psychiatric Rating

Scale (BPRS) for overall symptoms (Overall and Gorham, 1962), with the Scale for the Assessment of Positive Symptoms (SAPS) and with the Scale for the Assessment of Negative Symptoms (SANS) (Andeasen & Olsen, 1982). Mean BPRS score was 14.9 (SD = 6.25), and mean SAPS and SANS scores were 19.4 (15.7) and 33.6 (17.7), respectively. No one had a history of alcohol or other substance abuse, brain injury, or neurological disease. No participant had any medical illness known to affect brain function.

Ten healthy controls (5 females and 5 males) were recruited from the local community. Controls did not have any DSM-IV Axis I disorder, or a family history of psychotic illness. The mean SPQ score of controls was 14.3 (SD = 9.0). Healthy participants' mean age, education level, and IQ were 38.7 (SD = 7.2), 15.7 (SD = 2.7), 101.9 (SD = 11.8), respectively. These values were not significantly different from those of patients with schizophrenia (43.1(SD = 9.0), 15.0 (SD = 2.2), 100.6 (SD = 29.9)).

General social functioning was estimated using the Zigler social competence scale on the basis of each participant's demographic information. Ability of Theory of Mind (ToM) was also assessed with the Eyes Task (Baron-Cohen et al., 2001). Consistent with the previous experiments, a significant group difference was observed on both the Zigler scale and the Eyes Task between the two groups (see Table 5). Participants with a metallic or other magnetic sensitive medical device (e.g. pacemaker) in his/her body were excluded before imaging. The participants, all of whom had normal or corrected-to-normal vision were informed of the possible risks associated with MR, gave informed consent as approved by the Vanderbilt University Institutional Review Board, and were paid for their participation.

Table 5. The demographic data

	Control subjects (n = 10)	Schizophrenic subjects (n = 9)	*P*
Age	38.7 (7.2) [A]	43.1 (9.0)	n.s.
Education (years)	15.7 (2.7)	15.0 (2.2)	n.s.
WASI IQ Score	101.9 (11.8)	100.6 (29.9)	n.s.
BPRS	n/a [B]	14.9 (6.25)	
SAPS	n/a	19.4 (15.7)	
SANS	n/a	33.6 (17.7)	
SPQ	14.3 (9.0)	n/a	
Handedness (L/R/Ambi)	0/10/0	2/6/1	
Illness duration (years)	n/a	19.2 (9.2)	
Zigler score	6.1 (1.66)	3.56 (0.88)	< 0.01**
Eyes task [C]	25.1 (4.43)	19.0 (4.33)	< 0.01**

[A] Mean (standard deviation)
[B] Not applicable
[C] Revised version of the Reading the Mind in the Eyes Task (Baron-Cohen et al., 2001). All patients and 9 out of 10 controls were tested.

Stimuli

Biological motion (for localizer runs and event-related experiment) A series of PL biological motions created in the same way as the previous behavioral experiments were used. Animations were displayed using Matlab and the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997). All dots were black against a white background, and subtended approximately 6 arc min of visual angle with the average speed of 4 °/s. The entire point-light animation fell into a virtual rectangular region that subtended approximately 3.0×6.0 ° of visual angle. Animations consisted of 20 frames displayed over a 1 s period.

Scrambled motion (for localizer runs and event-related experiment) Scrambled motion sequences were created from the same motion vectors in the biological animations, by spatially randomizing the initial starting positions of the 12 dots. This scrambling was done in the same way as in experiment 2 and 3. Again, this procedure of

randomization left the motion trajectories of each dot intact but destroyed the spatial relations among the dots in the original biological motion sequence.

37% spatially scrambled motion (for event-related experiment only) A series of spatially 37% scrambled animations were created using the original biological motion sequences and 100% spatially scrambled motion sequences as in experiment 3. The initial position of each dot was determined by taking the position that divides the distance between the dot of biological motion and the corresponding dot of its scrambled motion into the ratio of 37:63. Therefore the hierarchical organization of the biological motion was broken but one could still find global similarity to the original biological motion. As mentioned previously, the reason 37%-scrambled motions were used is based on the results from experiment 3 in which the participants were asked to indicate the motion sequence that looked to be more biological when two differently scrambled motion sequences were presented at the same time. It was assumed that the range between 30% and 45% scrambling could include the threshold for successful perception of biological motion in schizophrenia. Because only one sequence was displayed in each trial in this study, the midway (i.e. 37%) between 30% and 45% scrambling was taken for the partially scrambled motion trials.

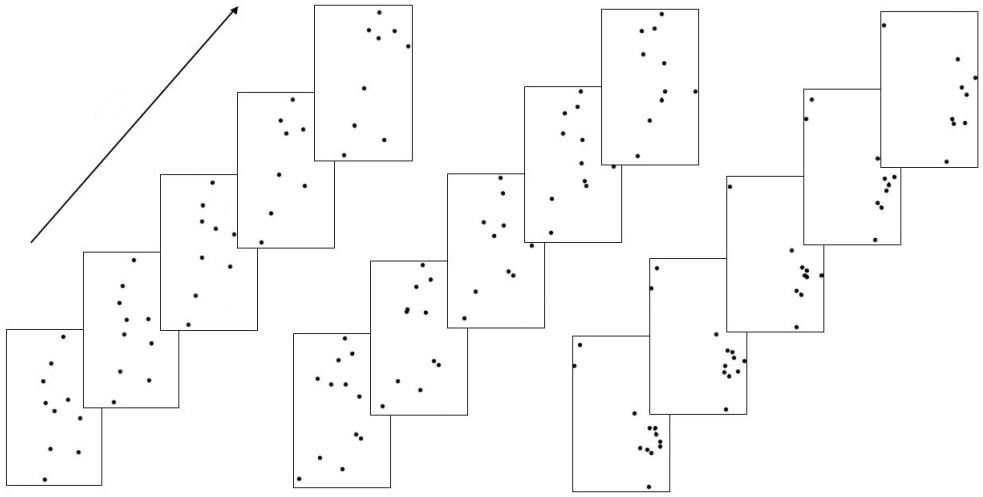

Figure 16. 5 frames (not successive) of a point-light walker as used in the biological, 37% scrambled, and completely scrambled motion trials. *Left:* A normal biological motion depicting stairway walking. *Middle:* 37% spatially scrambled motion created from the biological motion shown on the left. Each has a spatial position that divide the distance between "bio" position and "scrambled" position into 37:63. *Right:* A completely scrambled motion. Initial positions of the dots were determined by spatially randomizing the original positions of the dots forming the biological motion.

Optic flow and static dot field (for localizer runs only) In addition to the series of biological, scrambled, and 37%-scrambled motion animations, another motion stimulus was created, which consisted of 380 dots moving inward or outward from center of display (i.e. expansion or contraction) to simulate optic flow (Fig. 17). The dots subtending approximately 6 arc min of visual angle were colored black against a light gray background to minimize after-images. The entire array of dots fell into a virtual circular region subtending 13 ° of visual angle at the center of the screen. The static dot field had the same number of dots, but consisted of only 1 frame. These optic flow and static dot fields were used for localizer runs to functionally define motion sensitive area MT, compared to the STS which is selectively responsive to biological motion signals.

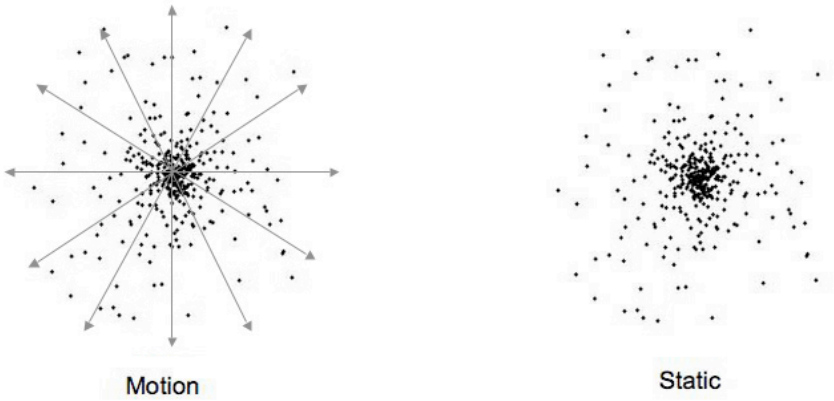

Figure 17. An 'optic flow' and static dot field consisting of 380 dots for functional localization of motion area MT

Procedure

Image acquisition All brain images were collected on a 3T GE Signa scanner located within the Vanderbilt University Medical Center (Nashville, TN). High-resolution T1 anatomical images were collected for each participant (170 slices, 1.0 × 1.0 × 1.0mm). Functional images (single-shot EPI, TR = 2000msec, TE = 25 msec, flip angle = 90°, matrix = 128 × 128, FOV = 240 × 240mm) were acquired over the whole brain, parallel to the anterior – posterior commissural (AC-PC) line (25 slices, 1.875 × 1.875 mm in plane, 4.5mm thick with 0.45mm gap). During the 1.5 hr scanning session, all participants completed three different types of functional runs: Two of which were for functionally localizing particular regions of interest (ROIs) (i.e. MT and STS), and the other was the main event-related run that was repeated 9 times. Localizer runs always preceded the event-related runs, and the order of the two localizers for defining MT and STS was counterbalanced across participants. Visual stimuli were presented using a DLP projector on a Macintosh computer. The projector's image was back-projected onto a

screen located at the observer's feet and viewed via a periscope mirror attached to the head coil.

Localizer experiments – STS and MT localization To functionally define the STSp ROI, the blood oxygen level dependent (BOLD) signals associated with viewing biological motion and scrambled motion were measured in a blocked design, and then compared for each participant. To do this, participants viewed alternating seven blocks of biological motion and seven blocks of 100% scrambled motion (Grossman et al., 2000). Blocks were temporally separated by 4 sec (2 volumes). Within each 14 sec block, seven 1 sec animations were presented with the interstimulus interval of 1 sec. To maintain the participant's attention during the scan session, each block included 1-back task in which participants responded with a button press whenever they found an animation that was the same as its previous one. The scan lasted 316 sec, the initial 8 sec (4 volumes) were discarded to allow for MR stabilization.

In addition to the localizer run for defining STS, participants were scanned with the MT localizer run in which 14 motion (optic-flow) blocks interleaved with 14 static blocks were presented. There were no blank periods between blocks. Because MT and STS are located closely, it was necessary to localize MT separately in each individual for clear localization of the STS. Another reason was based on past studies on motion perception in schizophrenia (Chen et al., 1999a,b; 2003b; Li, 2002; Stuve et al., 1997). Patients with schizophrenia also had deficits in perceiving non-biological, global motion signals, which strongly implicated area MT. Therefore, it is important to investigate whether MT activation would affect STS activation associated with biological motion perception.

During the scan session, observers were instructed to fixate at the center of the stimulus, and to press a button at every point of block switching in order to maintain their attention. The scan lasted 300 sec, and the initial 8 sec were discarded prior to analysis.

Event-related experiments During the scan session for the event-related runs, participants performed a biological motion discrimination task. One event run had 24 trials consisting of eight 1 s long biological motion, scrambled motion, and 37% scrambled motion sequences each. The interstimulus interval was 11 sec; this interval was long enough for individual BOLD response to return to resting state before the next trial (Bandettini & Cox, 1998). The three types of stimuli (biological, scrambled, and 37% scrambled animations) were presented in random order, and the observer's task was to judge whether the given motion depicted a human activity. Observers were given a 2 seconds time window for response following the stimulus offset. This task, therefore, was very similar to the task used in experiment 1, except that 37%- scrambled animations were added, and there was no 'correct' answer to these stimuli.

The event-related runs repeated 9 times. The total number of trials, therefore, was 216. Participants took a rest, if necessary, between runs.

Image analysis Imaging data were preprocessed and analyzed using Brain Voyager QX 1.9 (Brain Innovations, Maastricht, The Netherlands). The anatomical volumes were transformed into a stereotactic space that was common for all participants (Talairach & Tournoux, 1988). Functional volumes for each participant were aligned to these transformed anatomical volumes. Functional volumes were also pre-processed following

procedures including image realignment, three-dimensional motion correction, linear de-trending, temporal frequency filtering with high pass filter, and spatial smoothing with a 4 mm FWHM spatial filter.

To isolate ROIs of STSp that were significantly more engaged by biological motion than scrambled motion signals, the single-study general linear model (GLM) was applied to time-series of task-related function volumes for each individuals. Individual-specific ROIs were then isolated by first identifying the peak voxel in an area of interest that was significantly activated by biological motion over scrambled motion. This was completed by subtracting activation to scrambled motion from activation to biological motion, using a voxel-wise analysis thresholded at $p < 0.01$, Bonferonni corrected, or at a false discovery rate (FDR) of $q < 0.05$, when activation was not present at the first threshold. ROIs were then defined around the resulting peak and included all significant voxels above threshold. The same analysis was applied to define area MT, by subtracting activation to static dot field signals from activation to optic-flow stimuli.

To analyze the data from event-related functional runs, the design matrix (reference time course) was defined to include 4 predictors on the basis of each individual's behavioral response: (1) activation when an observer made "hits" ("biological" responses to biological motion, termed "Bio-Bio" in results section), (2) "correct rejection" ("scrambled" responses to scrambled motion, "Scram-Scram" in results), (3) "false alarms" ("biological" responses to scrambled motion, "Scram-Bio" in results), and (4) activation to 37% scrambled motion regardless of responses ("37% Scram"). The last predictor was divided into two categories according to the subjective responses in a follow-up analysis. Within these defined ROIs, the voxels coupled with the event-related

trials were averaged to create a single time series for each condition (predictors) in each individual. MR signal levels coupled with each condition were averaged to create an estimate of BOLD activity through the process of event-related averaging in the BrainVoyager QX. Percent change in BOLD signal associated with each condition was defined as the difference between "baseline" (activation at the stimulus-onset) and the peak activity over time.

Results

Behavior Analysis

Discrimination between biological and scrambled motion The behavioral task during the event-related functional scans was to judge whether the given motion in each trial depicted human activity. Three types of stimuli (biological, scrambled, and 37% scrambled animations) were presented in random order. Participants had 2 sec to respond following the stimulus presentation. Patients with schizophrenia failed to respond significantly more times across all types of stimuli, compared to normal controls. Missing response rates for biological, scrambled, and 37% scrambled motion were 31.4%, 35.8%, and 31.7% in schizophrenia while healthy controls had the rates of 6.1%, 9.0%, and 6.98%, respectively. The difference was statistically significant (biological: $t(17) = 2.74$, $p < 0.02$; scrambled: $t(17) = 2.57$, $p = 0.02$; 37% scrambled: $t(17) = 2.36$, $p < 0.05$), and the trials missing responses were excluded in analyses of behavioral and imaging data.

Similar to the experiment 1, the number of "hits" and "false alarms" were counted to calculate an unbiased measure of sensitivity, d'. Only the trials with biological and 100% scrambled motion were included to derive d' because there was no correct answer to the

37% scrambled motion other than a subjective decision. Mean (SE) *d′* values are shown in Fig. 18. Consistent with the results from experiment 1, the patients' discrimination between biological motion and scrambled motion was significantly worse than that of normal controls (2.62 (0.53) vs. 4.18 (0.39), $t(17) = 2.38$, $p < 0.03$). Fig. 19 shows mean (SE) hit-rate and false alarm-rate in the two groups. Also similar to the results from experiment 1, the two groups showed comparable hit-rate to each other, 94.12% in schizophrenia and 98.38 in controls ($t(17) = 1.47$, $p = 0.16$), whereas the patients had a higher false-alarm rate (40.79 (10.52)%) than controls (19.7 (5.8) %), indicating that the lower *d′* observed in schizophrenia patients is mainly due to their higher false alarm rate. However, the difference in false alarm-rate just missed significance ($t(17) = 1.81$, $p = 0.089$). This tendency did not reach significance probably because of the small number of participants. However, the actual effect size was large (Cohen's $d = 0.82$).

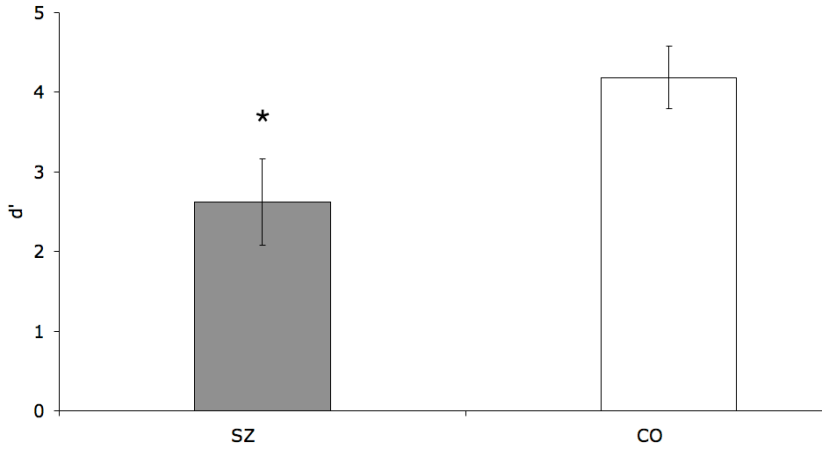

Figure 18. *d′* on the discrimination task during functional imaging. * $p < 0.05$

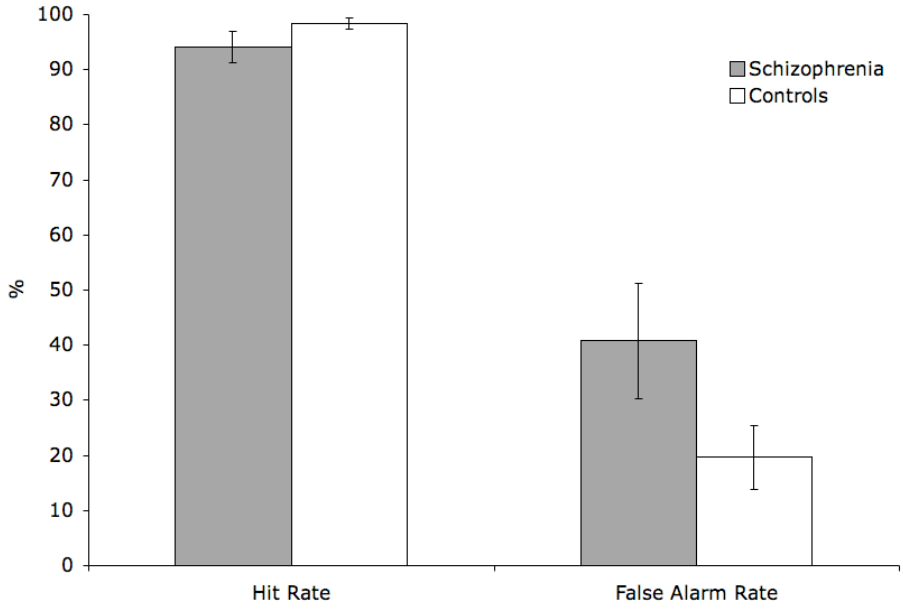

Figure 19. Hit-rate and False-alarm rate in discrimination of biological motion

Subjective response to 37% scrambled motion Based on the results from experiment 3 (discrimination of partially scrambled biological motions), and in particular from the condition of 30% vs. 45% scrambled animations where patients with schizophrenia recorded chance accuracy (Fig. 20), it was expected that perception of 37% scrambled animations would be very different between the two groups. That is, the patients were expected to perceive these animations as biological or scrambled motions with a similar probability, while controls would have stronger bias. However, the actual result revealed that most observers regarded these 37% scrambled animations as scrambled motion. The patients, however, still responded "biological motion" to these stimuli in more trials than controls, as shown in Fig. 20. Although the difference did not reach statistical significance ($t(17) = 1.52$, $p = 0.15$), the results from the 37% scrambled biological

motion trials are consistent with the higher false alarm rate in 100% scrambled motion trials in schizophrenia.

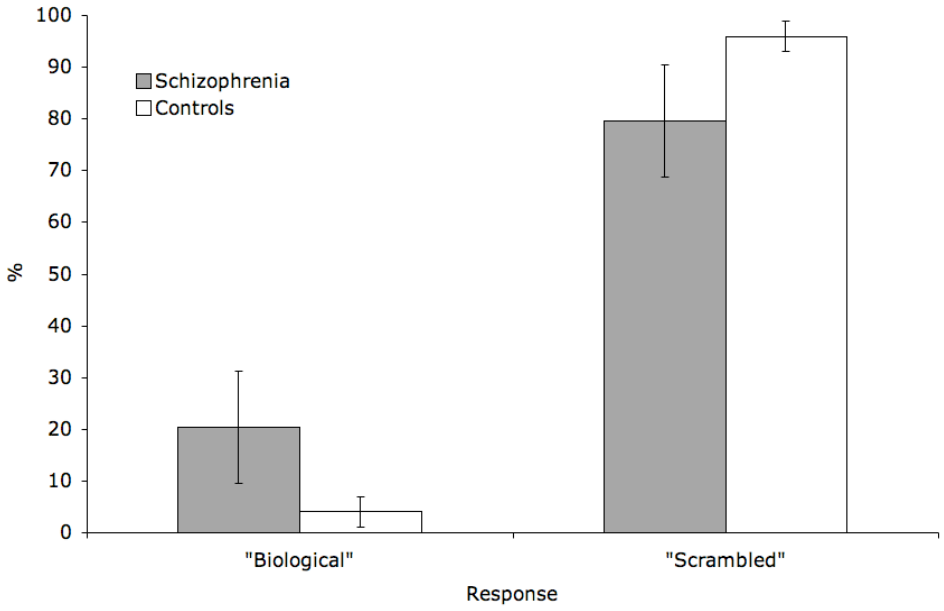

Figure 20. Subjective responses of "Biological" or "Scrambled" to 37% scrambled motion sequences.

Correlation with demographic information and social functioning In the patient group, the symptom severity measured with BPRS, SAPS, and SANS was not significantly correlated with *d′* values, which is similar to previous experiments. Demographic variables (age, education level, or IQ) were not correlated with behavioral performance on the task in either of the patient group or control group. SPQ score in controls was not correlated with *d′* values. For all participants, the correlation between social functioning estimated by the Zigler scale and the Eyes task did not reach significance (Zigler- *d′*: r = 0.34, p = 0.14; Eyes task- *d′*: r = 0.38, p = 0.13).

Brain Imaging Results

One patient was excluded from analysis because her imaging data were statistical outliers when normalized. Therefore, eight patients with schizophrenia and ten healthy controls were included.

Localizer experiment Two ROIs were functionally localized through the localizer runs during the imaging session: bilateral posterior superior temporal sulcus (STSp) (biological motion vs. scrambled motion) and bilateral motion sensitive area MT (optic flow vs. static dot field). In the schizophrenia group, STSp was localized in six out of eight observers by comparing activations to the biological motion block and to the scrambled motion block. For the remaining two patients, their STSp ROIs were defined through observing areas that were activated by biological motions only and then comparing those areas with the group-defined ROI from the other six patients. The STSp of those two patients were activated during the biological motion block and were located in approximately the same Talairach coordinates as others', but were also equally activated by scrambled motion animations. STSp was found unilaterally in the right hemisphere of four of the eight patients, and bilaterally in the other four patients. In the control group, STSp was localized successfully in all observers; three of them showed unilateral activation in the right hemisphere and the other seven had bilateral activation. The right hemisphere dominance found in this localizer study is consistent with previous reports using similar conditions (Pelphrey et al., 2003; Grossman et al., 2000). Area MT was localized in all participants; one control and one patient showed unilateral activation in the right hemisphere and in the left hemisphere, respectively. Mean (SD) Talairach

coordinates are given in Table 6. The mean coordinates were similar to those of a previous study (Grossman et al., 2004).

Table.6. Talairach coordinates of the defined ROIs

		Talairach Coordinates					
		Left hemisphere			*Right hemisphere*		
	ROI	*x*	*y*	*z*	*x*	*y*	*z*
CO	STSp	-51.8 (4.9)	-55.9 (10.9)	10.3 (6.5)	49.5 (7.6)	-53.5 (8.9)	9.6 (5.3)
	MT	-43.2 (4.2)	-69.1 (5.0)	-0.9 (5.0)	44.1 (1.9)	-63.8 (5.6)	-0.7 (6.1)
SZ	STSp	-53.5 (9.7)	-50.5 (9.6)	9.3 (5.6)	46.0 (8.9)	-55.0 (11.7)	9.5 (5.7)
	MT	-43.4 (6.6)	-69.3 (6.2)	-1.4 (5.1)	40.6 (3.4)	-66.0 (4.2)	-3.14 (5.8)

Mean coordinates and standard deviations (in parentheses) for the two ROIs (posterior STS and MT) in each group. CO: controls, SZ: schizophrenic patients.

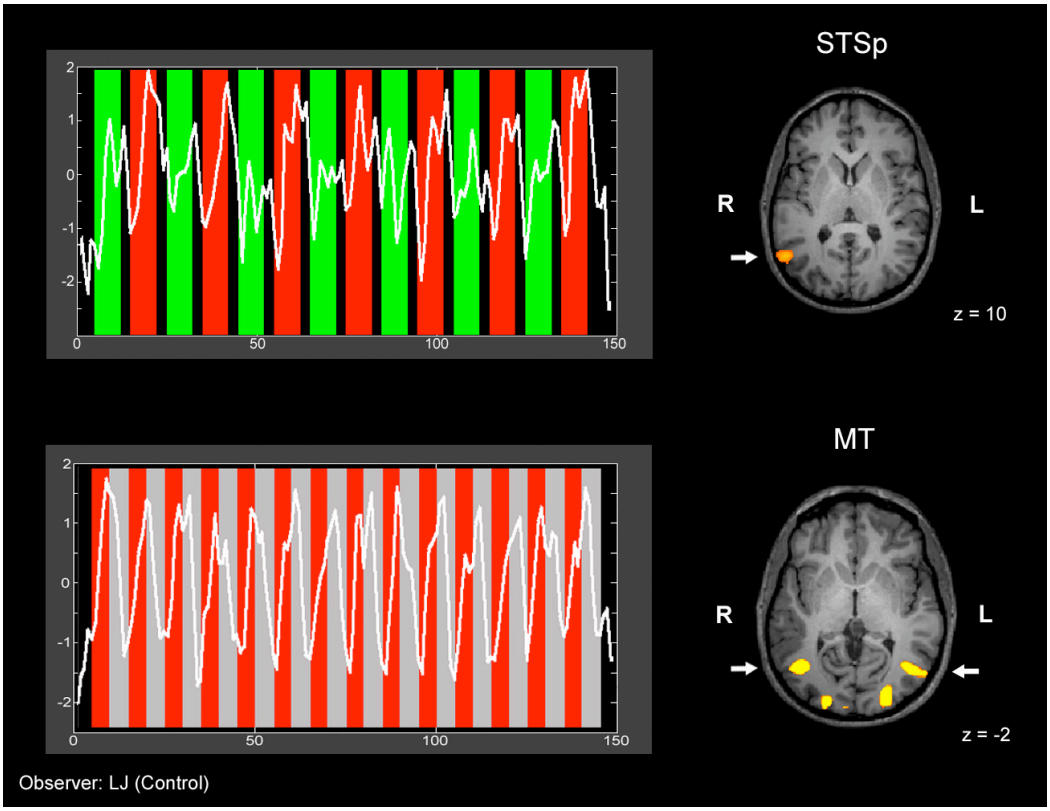

Figure 21. ROIs in one example observer. Top: BOLD activity plot of the time course from the right STSp ROI and the horizontal view of the STSp in the right hemisphere (left hemisphere is on right, and right hemisphere on left). Red bars indicate 14 sec lasting biological motion block and green bars are scrambled motion block. Bottom: BOLD activity plot of the time course from the right MT ROI from the same observer and the horizontal view of the bilateral MT (activated area in anterior and lateral regions on the slice). Red bars indicate motion blocks (optic flow) and gray bars are the blocks of static dot field.

Event-related fMRI experiment As described in the previous section, imaging data collected during 9 event-related runs were analyzed based on the type of stimulus presented and the observers' behavioral response, including "hits (Bio-Bio)", "correct rejection (Scram-Scram)", "false-alarms (Scram-Bio)", and all responses to 37% scrambled motion. These four categories were defined as the four response conditions for analysis. "Miss" ("scrambled motion" response to biological motion) trials were not analyzed because the numbers of trials were minimal in both groups. As for the trials of 37% scrambled motion, as shown in Fig. 19, most participants judged these animations as nonbiological, scrambled motion sequences. Therefore, the data of BOLD signal change to 37% scrambled motion were collapsed regardless of participants' responses.

Event-related activities in the posterior superior temporal sulcus (STSp) Averaged BOLD activities across observers are shown in Fig. 22. BOLD change was defined as the difference (percent change) between the peak of BOLD response and the baseline BOLD activity at the moment of stimulus onset (Fig. 22 A, B).

For overall activation within the STSp ROI in each response condition (Fig. 22 C), multifactorial repeated measures ANOVA was conducted: The main effect of diagnosis (group) was not significant ($F(1,27) = 0.53$, $p = 0.47$), indicating overall STSp activation was not different between groups when activations to 3 types of stimuli were included. The main effect of response conditions (i.e. hits, correct rejection, false alarms, and response to 37% scrambled motion) was not significant ($F(3,81) = 2.15$, $p = 0.10$). However, ANOVA revealed a significant interaction effect of group × response conditions ($F(3,81) = 3.98$, $p < 0.02$), indicating healthy controls and schizophrenia

patients showed different patterns of BOLD signal change to different motion stimuli and/or according to their perception. Normal controls showed greater activation within STSp in "Bio-Bio" and "Scram-Bio" categories while weaker activation in "Scram-Scram" and to the 37% scrambled motion. Note that in over 95% of trials normal controls judged 37% scrambled motion as just scrambled motion. These results in the control group suggest that normal people show greater STSp activation when they "perceive" biological motion signals, whatever the actual stimulus is.

On the other hand, patients with schizophrenia did not show such strongly modulated activation according to their response. In fact, patients showed relatively greater activation to scrambled motion (Scram-Scram) and to 37% scrambled motion (again, note that 80% patients judged it as scrambled motion) than healthy controls. When only the two response conditions (Bio-Bio and Scram-Scram) were considered, the group × conditions interaction effect was quite significant ($F(1,27) = 10.32$, $p < 0.005$).

Event-related activities in area MT The same procedure of analyses was also applied to the bilateral MT. Repeated measure ANOVA revealed the main effect of diagnosis (group), indicating that the patients' BOLD signal change in bilateral MT is significantly smaller than that of normal controls ($F(1,32) = 7.42$, $p = 0.01$), as shown in Fig. 23. The main effect of response condition was also significant; MT activation across the two groups was greater in 'hits' and 'false alarms' in general ($F(3,96) = 3.24$, $p < 0.03$) because of lower activation to 37% scrambled motion in both groups. Without this category, the main effect disappeared ($F(2,64) = 0.82$, $p = 0.45$). However, the interaction between the group and response conditions was not significant ($F(3,96) =$

1.18, p = 0.32), indicating that both schizophrenia patients and controls had similar activation patterns according to responses.

Correlation between BOLD signals in STSp and MT Another possible question is whether activation within MT would affect or modulate activation in STSp area to biological or scrambled motion stimuli. Therefore, correlations between MT activation and STSp activation to each response condition were examined within each group, in all participants, unilaterally and bilaterally. None of the correlations were significant.

STSp activation to 37% scrambled biological motion Most of the controls and patients judged 37% scrambled motion as scrambled motion. However, in 4% (24 trials, in controls) and 17.5% (76 trials, in patients) of the included trials the observers responded as "biological motion." Therefore, it was necessary to investigate STSp activation to "biological" responses to 37% scrambled motion, although the number of these trials was small. The results are shown in Fig. 24, which are consistent with the results from analyses of the other three response conditions. That is, normal controls showed greater STSp activation when they subjectively perceived a given stimuli as "biological". However, schizophrenia patients did not show different activation between the two subjective responses or slightly greater activation when they responded "scrambled". But total number of trials of "biological" response for each group was so small. Therefore, these results were not further analyzed statistically.

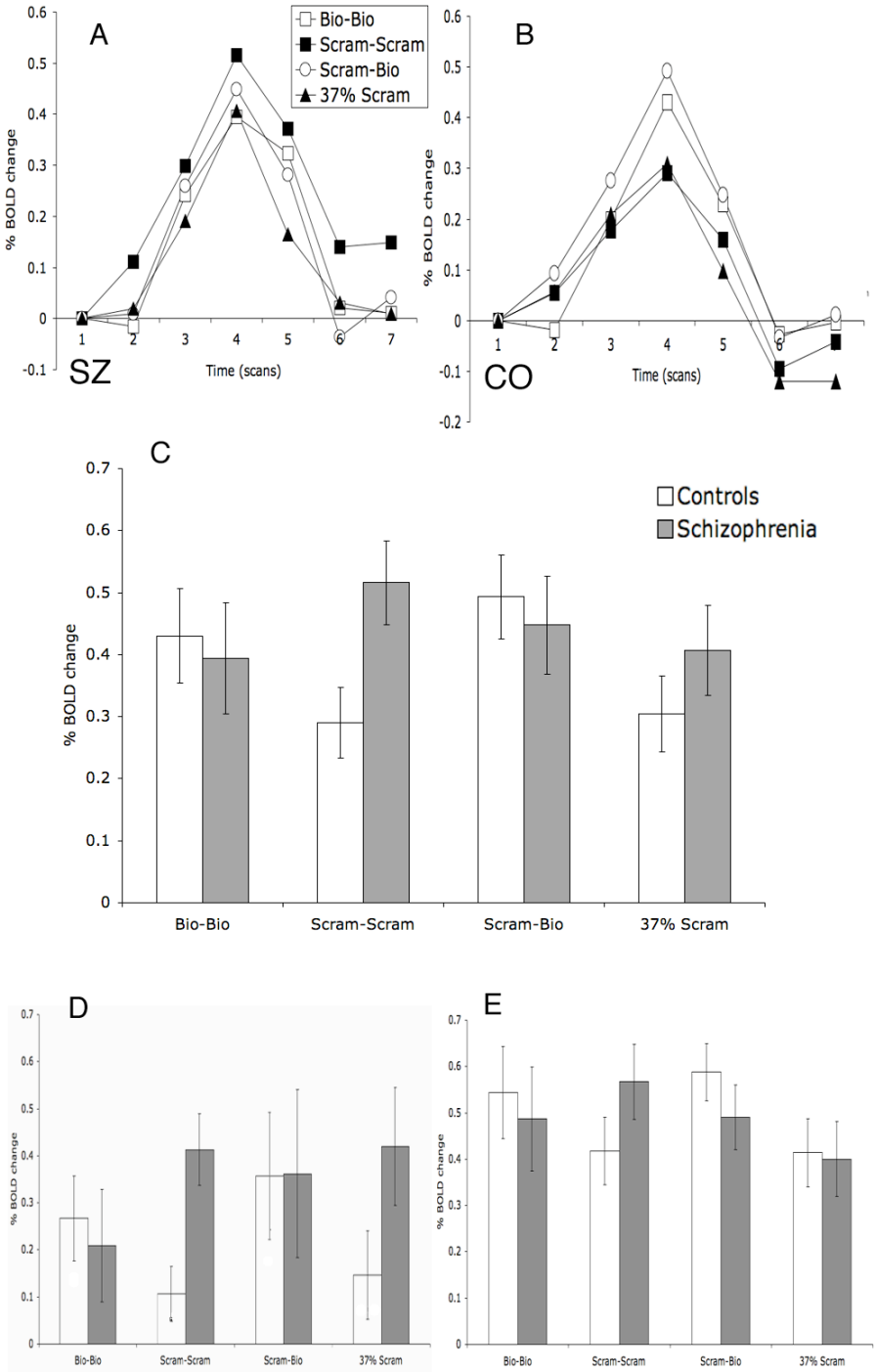

Figure 22. Average peak BOLD activity across observers in STSp ROI. A: Averaged BOLD activities along the scans in schizophrenia. B: Averaged BOLD timecourse in controls C: Mean peak STSp activations in left and right hemisphere. D: Mean peak STSp activation in left hemisphere. E: Mean peak STSp activation in right hemisphere. "Bio-Bio" indicates *hits* ("biological" response to biological motion). Similarly, "Scram-Bio" means false alarms ("biological" response to scrambled motion). "37% scram" includes both 'biological' and 'scrambled' responses. BOLD change is shown as the difference (%) between the peak and the baseline defined as the activity at the stimulus onset.

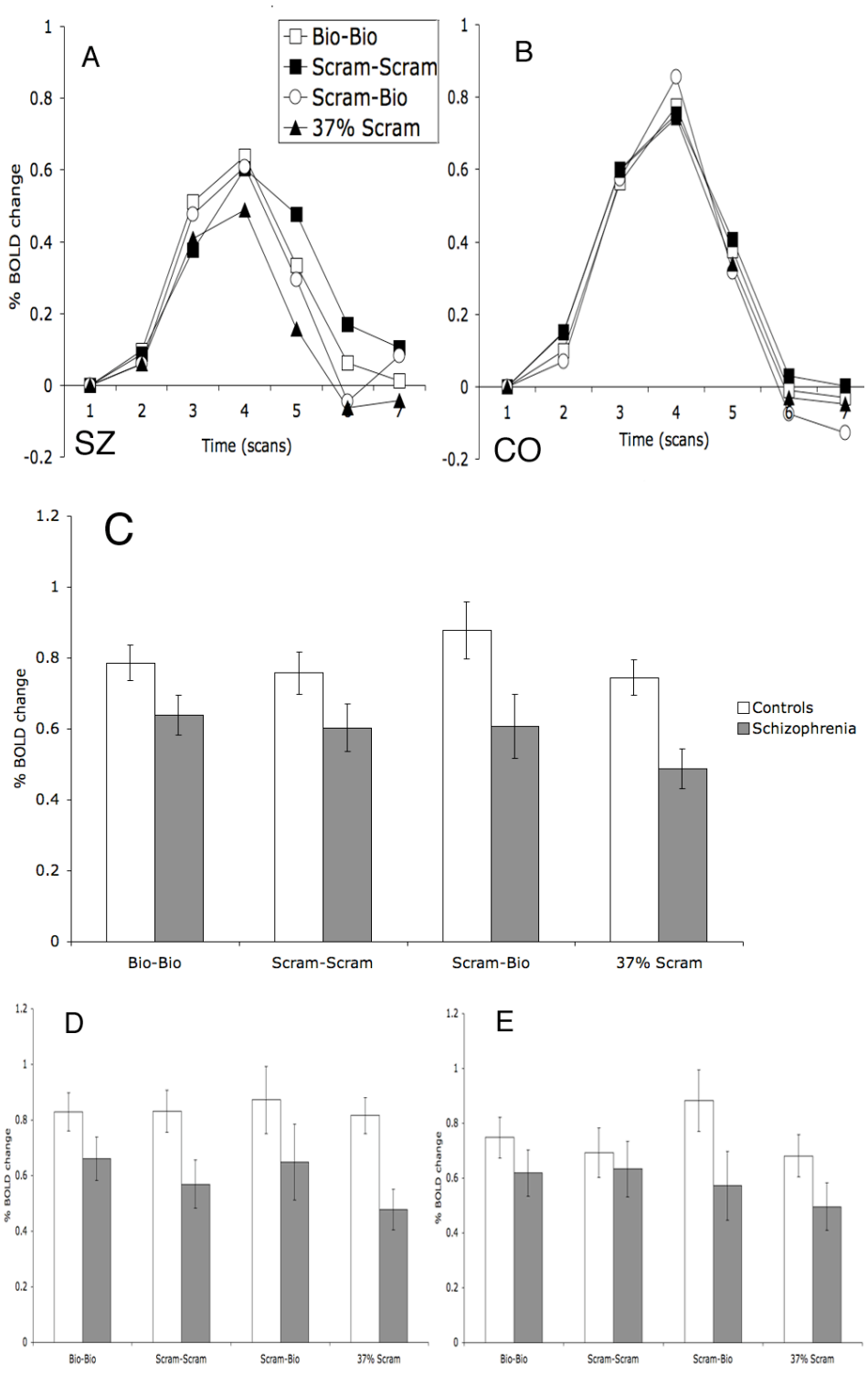

Figure 23. Average BOLD activity across observers in MT ROI. A: Averaged BOLD activities along the scans in schizophrenia. B: Averaged BOLD time course in controls C: Mean peak MT activations in left and right hemisphere. D: Mean peak MT activation in left hemisphere. E: Mean peak MT activation in right hemisphere.

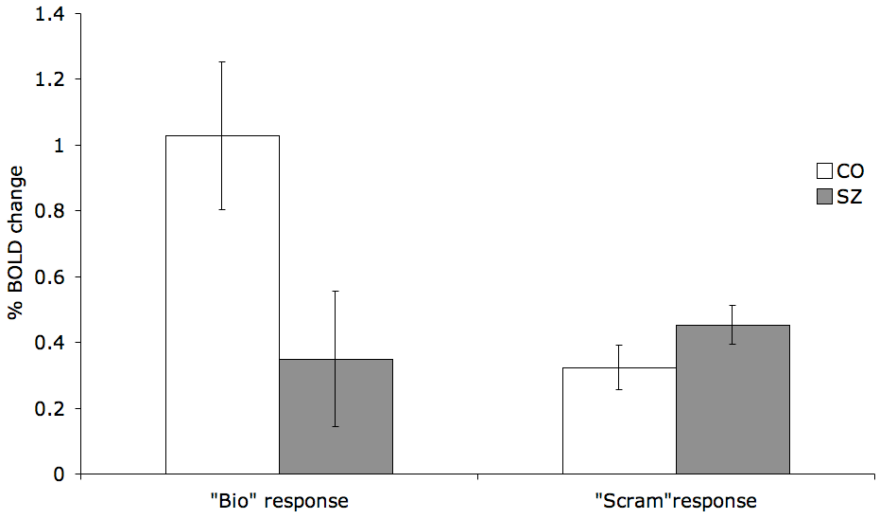

Figure 24. BOLD signal change (peak values) according to subjective "biological" or "scrambled" responses to 37% scrambled motion stimuli. Error bar indicates 1 standard error of means.

Correlations with symptoms, demographic variables, and estimated social functioning Correlations were investigated among the demographic variables, symptom severity, social functioning scores, behavioral performance, and BOLD signals within the STSp, in each group and in all participants. Demographic variables such as age and education level did not affect imaging results. In all participants, social functioning measured with the Zigler scale and Eyes task had a negative correlation with the STSp activation in the left hemisphere to scrambled motion (including 37% scrambled motion), suggesting higher social functioning was correlated with weaker activation to non-biological motion in left STSp (Zigler scale: $r = -0.69$, $p < 0.05$; Eyes task: $r = -0.68$, $p < 0.05$). Individuals with better performance on discrimination showed weaker STSp activation to scrambled motion ($r = -0.53$, $p < 0.05$). Symptom severity in patients seemed to have a correlation with activation in left STSp. However, left STSp was localized in only 4 patients. Correlation results are summarized in Table. 7.

Table. 7. Correlations

Group	*Correlation*	*hemisphere*	*r*	*p*	*N*
All	Zigler score – Eyes Task score		0.72	<0.01**	16
	Zigler score – STS activation to scrambled motion	Left	-0.69	<0.05*	11
	Eyes Task score – STS activation to 37% scrambled motion	Left	-0.68	<0.05*	9
	d′ - STS activation to scrambled motion	Bi	-0.53	<0.05*	18
SZ	BPRS score – STSp activation to scrambled motion	Left	0.97	<0.05*	4
	SAPS score – STSp activation in false-alarm trials	Left	0.96	<0.05*	4
CO	SPQ score – STSp activation difference b/w biological motion and false-alarm trials	Right	-0.64	<0.05*	10

Zigler score: estimate of global social functioning
Eyes task score: estimate of ability of Theory of Mind (ToM)
BPRS score: overall symptom severity of schizophrenia
SAPS score: positive symptom severity of schizophrenia
SPQ score: index of schizotypal personality in healthy controls
SZ: Schizophrenia
CO: Controls

Discussion

This experiment investigated activations within STSp and MT to biological motion, scrambled motion, and partially (37% spatially) scrambled motion sequences using a discrimination task similar to the task used in experiment 1.

Analysis of behavior Analysis of behavioral performance during functional scanning revealed that *d′* values of patients with schizophrenia were significantly lower than that of controls, confirming the results from experiment 1. In addition, this lower mean *d′* value in schizophrenia was caused by a higher rate of false alarms. The result from 37% scrambled motion trials was not as expected: patients' responses were expected to be divided into "biological" and "scrambled" equally, considering their chance accuracy in discriminating 30% and 45% scrambled motions in experiment 3. However, in most trials (96% in controls and 84% in schizophrenia), the participants judged these stimuli as non-

biological or scrambled motion. The reason for this response bias may be due to the task design. The task in the present experiment neglected the possibility that participants' decision would be different when only one partially scrambled motion is presented and simple categorization is required. As a result, the participants' absolute judgment appeared very different from their relative discrimination in experiment 3. Regardless, it is interesting that the patients still showed a higher rate of judging 37% scrambled motion as 'biological motion' when compared to normal controls.

Another issue in the behavioral result is the average d' value. The control participants' mean d' value in this experiment was much higher than the d's in experiment 1. This might be an outcome of different methods of scrambling. Experiment 1 used a series of scrambled motions that were randomized in spatial location of each dot, as well as, a temporal phase. On the other hand, only spatially scrambled motions were used in the current experiment. Therefore, the task difficulty could be considerably different between the two experiments. Still, there was a significant difference in d' values between the two groups, and the patients perceived 37% scrambled motion as biological motion in more trials. All of these findings indicate that patients' "deficit" in biological motion perception is robust.

Localizer study The localizer experiment succeeded in functionally localizing ROI STSp from all controls, and from 6 out of 8 patients, by subtracting activations during scrambled motion blocks from biological motion blocks. Although the goal of the localizer study was to identify ROIs (STSp and MT) prior to data analysis of the event-related functional runs, this result could be also regarded as a finding in itself and

suggests a lack of differential activation to biological and scrambled motion in schizophrenia patients.

Event-related experiment: Normal control group In the main event-related experiment, normal controls showed greater STSp activation when they correctly perceived biological motion ("hit" or "Bio-Bio" condition) than when they correctly perceived scrambled motion as scrambled motion ("correct rejection" or "Scram-Scram" condition). This observation actually repeated the results from the localizer experiment and, therefore, provides another piece of confirmative evidence that STSp is selectively responsive to biological motion in normal controls. This result is also supported by past research arguing that familiar forms of motion signals, such as biological motion, can be processed very efficiently and almost effortlessly (Ahlström, Blake, & Ahlström, 1997; Johansson, 1973; Neri, Morrone & Burr, 1998; Pavlova & Sokolov, 2000; Sumi, 1984). That is not all: Control participants also showed strong STSp activation to scrambled motion to which they responded 'biological motion' (false-alarm). This is an interesting result because it indicates that STSp activation is associated with observer's response (subjective perception), rather than the features of stimuli. Increased STSp activation in false-alarm trials, therefore, implicates that some form of high-level, top-down processing is involved in biological motion. Although there were only a few trials (4%) in which observers responded 'biological' in the 37% scrambled motion condition, STSp activation in this condition was also clearly divided according to observer's response.

As discussed in experiment 3, there have been several studies suggesting the role of top-down processing in biological motion perception (Cavanagh et al., 1991, Cavanagh et

al., 2001; Dittrich, 1993; McLeod et al., 1996; Thornton et al., 2002;Vaina et al., 1990). For example, Dittrich (1993) suggested that efficiency of biological motion processing is strongly influenced by action categories. That is, more familiar actions such as walking are generally recognized faster and more accurately than other actions such as greeting. So he proposed that "selective movement filters" enhance recognition of familiar biological motion. Similarly, Cavanagh et al. (2001) proposed a set of operators called "sprites", which is "the set of routines responsible for detecting a specific characteristic motion in the input array, for modeling and animating the object's changing configuration, and for filling in the predictable details of the motion over time". These hypothetical top-down mechanisms are thought to work by combining knowledge-based, semantic information about human action with spatiotemporal motion information (Thornton & Rensink, 2002). Bertenthal and Pinto (1994) have argued that the processing of global form of biological motion, specified by motion, precedes the perception of individual elements and their relations. Consistent with this hypothesis, Shiffrar and colleagues found that biological motion is readily perceivable even when viewing through multiple apertures (Shiffrar, Lichtey, & Heptulla-Chatterjee, 1997) , and this finding has been confirmed by imaging results (Beauchamp et al., 2002; Blakemore et al., 2003; Pelphrey et al., 2003). Thompson and colleagues (2005) found that the inferior temporal sulcus (ITS) was strongly activated by an intact biological walker than a fragmented version of the walker. The ITS has been implicated in object recognition (Malach et al., 1995; Pietrini et al., 2004), visual imagery (Ishai, Ungerleider, & Haxby, 2000), and configuration of object shape (Kourtzi & Kanwisher, 2001). Thompson and colleagues, therefore, suggested that the ITS may interact with the STS to enable

biological motion recognition. If so, the strong STSp activation in false-alarm trials could reflect that input from the ITS that may have been erroneously activated by scrambled motion. Whatever the exact mechanism is, the current results from the event-related imaging in healthy individuals clearly show that STSp activation is coupled with observers' own perception, not only with the features of stimulus, influenced by top-down processing. In addition, strong STSp activation in false-alarm trials may reflect 'error' of those top-down mechanisms in normal observers.

Event-related experiment: Schizophrenia patients Patients with schizophrenia, on the other hand, showed a different pattern in STSp activation. First, the patients' STSp activations to biological motion (Bio-Bio) and to false-alarm trials (Scram-Bio) were similar to those of controls. However, activation to scrambled motion (Scram-Scram) was significantly greater than in normal controls. Second, the patients' STSp was more activated in the 37% scrambled motion trials than that of controls, although the group difference was not significant. Third, within the 37% scrambled motion condition, patients' STSp activation was not modulated by their response. Taken together, STSp activation in the schizophrenia group did not differ across the types of stimuli or subjective responses, whereas controls had greater activation when they subjectively perceived biological motion. This resulted in relatively greater STSp activation to scrambled motion (Scram-Scram) in schizophrenia. Thus, this unexpectedly greater activation to scrambled motion is a new finding from this experiment (it is more intuitive and natural to expect weaker activation to biological motion if we consider the general definition of "deficit" in schizophrenia).

The exact reason for greater STSp activation to scrambled motion is unknown for now. However, this unexpected greater activation could be interpreted in two ways: a passive neural process or an active neural process. In either case, the basic assumption is that the STSp strongly responds to *biological motion, including subjectively perceived ones*, as indicated by similar level of activation in "hits" and "false alarms" between groups. Therefore, this default or primary function of the STSp area may be functional in both populations. "Passive" processing of scrambled motion means that the patients may simply have failed to filter irrelevant stimuli. That is, the STSp might have been passively and unnecessarily activated by non-biological motion, failing to inhibit activation. This interpretation reminds us again of deficits in sensory gating or filtering input array (Braff et al., 1992; Green et al., 1994b) as discussed in experiment 3. "Active" processing means that the patients could activate STSp to process biological motion properly, but they may need extra resources for successful 'rejection' of an irrelevant stimulus (stronger activation to scrambled motion in 'correct rejection' trials). This hypothetical active process may depend more on top-down processing, which is closely related with frontal function. Although the reason for greater activation to scrambled motion in schizophrenia is unknown, the STS dysfunction could be defined as normal activation for biological motion perception but abnormally stronger activation to scrambled motion, resulting in poorer ability to discriminate and detect biological motion signals, on the basis of the current results.

There seems to be some correlation between the abnormally greater STSp activation to scrambled motion and overall schizophrenic symptom severity, as described in Table 7. However, it is uncertain because the correlation was observed from activation in the left

hemisphere which was localized from only 4 patients. It will be necessary to investigate this relationship with more patients in future studies.

Area MT Another finding came from activation to biological motion and scrambled motion within MT area. Patients with schizophrenia showed weaker activation throughout all response conditions, indicating that patients' MT is also functionally compromised in processing visual motion signals compared to normal controls. MT dysfunction has been strongly suggested by findings of impaired velocity discrimination and coherent motion perception in schizophrenia for the last decade (Chen et al., 1999a,b; Chen et al., 2003; Li, 2002; Stuve et al., 1997). MT activation observed in the patient group in the current study may provide confirmative evidence for impaired general motion perception and corresponding MT dysfunction in schizophrenia. After all, the PL animations portraying biological motion or scrambled motion are also a type of global motion signals. Therefore, this significantly weaker activation within MT area suggests the possibility that patients with schizophrenia did not process the primitive motion signals successfully and efficiently at the stage of MT. Then, one may ask if these reduced MT activations could eventually disturb perception of biological motion in schizophrenia patients. This seems unlikely. First, there was no correlation between MT activation and STS activation in patients or in controls. Second, the MT activation was not modulated by the stimulus type (biological, scrambled, partially scrambled) or by response pattern (hit, correct rejection, false-alarm) as observed in normal STSp. Within each group, participants showed a similar level of activation in MT area across the conditions of stimuli and responses, regardless of significant group difference in

activation. Third, past physiological and lesion-case studies (Battelli, Cavanagh, & Thornton, 2003; McLeod et al., 1996; Schenk and Zihl, 1997a,b; Vaina et al., 1990; Zihl, von Cramon, & Mai, 1983) provided compelling evidence that the processes underlying biological motion perception and coherent, translational motion perception may be dissociated. The finding in the current study provides confirming evidence for these past case (lesion) studies.

Correlations Analyses of correlations with symptoms and social functioning are not decisive because there were not enough participants to pull out correlation data. However, still some interesting correlations were found; for all participants, better discrimination between biological and scrambled motion (i.e. *d′* values) were negatively correlated with STSp activation to scrambled motion. Individuals with higher Zigler scores also showed lower STS activation to scrambled motion, suggesting again the possible association between social functioning and biological motion perception. However, the Eyes task scores were not significantly correlated with STS activation in any condition.

Summary and conclusion To summarize, the present fMRI experiment confirmed 1) differential STSp activation to biological motion and to scrambled motion in normal controls, 2) a difference in activation within area MT between schizophrenia and controls, suggesting general dysfunction of motion processing in schizophrenia. The novel results of the present study include: 1) STSp activation to biological motion depends on healthy observer's subjective perception, whatever the actual stimulus is, which suggests the role of top-down processing, 2) Such modulated activation is not observed in patients with

schizophrenia. Rather, they show greater activation to scrambled motion compared to normal controls. The reason is unknown, but it is possible that the patients may have difficulty filtering irrelevant stimuli or may require an extra resource to identify non-biological motion successfully. The absence of a correlation between MT activation and STSp activation provides additional evidence of dissociated processing of biological motion and coherent, translational motion in both healthy individuals and individuals with schizophrenia.

CHAPTER V

AN EXPANDED STUDY:VISUAL PERCEPTION, INCLUDING BIOLOGICAL MOTION PERCEPTION, IN OBSESSIVE-COMPULSIVE DISORDER

In the previous experiments described in CHAPTER III and IV, the deficit in biological motion perception was observed and its underlying neural mechanisms were investigated in patients with schizophrenia. Interestingly, similar perceptual deficits have already been observed in another clinical population: children with autism, who show impaired recognition of biological motion, but intact perception of global form (Blake et al., 2003). Both patients with autism and schizophrenia are characterized by impaired social functioning (Frith & Frith, 1999), and the negative symptoms of schizophrenia often yield similar behavioral characteristics as those observed in autism. There is also evidence indicating clinical and behavioral similarities between schizophrenia and obsessive-compulsive disorder (OCD) (Berman, Kalinowski, Berman, Lengua, & Green, 1995; Bland, Newman, & Orn, 1987; Borkowska, Pilacynska, & Rybakowski, 2003; Lysaker, Lancaster, Nees, & Davis, 2004; Shin et al., 2008). Although the ability of ToM in OCD patients is unknown, OCD patients are also characterized by impaired social skills that compromise the quality of life (Bystritsky et al., 2001). These similarities in autism, schizophrenia, and OCD raise the question of whether OCD patients have similar deficits in their visual perception. Therefore, as an expanded study, CHAPTER V focuses on whether OCD patients have deficits in visual perception, including perception of biological motion. In the next section, a brief overview of the perceptual and cognitive characteristics of OCD is addressed along with the purpose of the experiment.

Experiment 5. Visual motion perception in obsessive-compulsive disorder

Obsessive-compulsive disorder is a debilitating psychiatric condition affecting about 2% of the population, and is characterized by recurrent, intrusive thought (obsession) and repetitive, ritualistic behaviors (compulsion). These characteristics lead to severe distress, anxiety and interfere with daily functioning and social activities (American Psychiatric Association, 1991). The symptom of obsession is known to interfere with cognition and can cause severe anxiety, and compulsions are maladaptive behaviors that reduce anxiety associated with obsession.

When studied using standard neuropsychological tests, OCD patients exhibit a variety of cognitive and perceptual impairments, including deficits in memory (Boone, Ananth, Philpott, Kau, & Djenderedjian, 1991; Christensen, Kim, Dysken, & Hoover, 1992; Savage et al., 1999) and executive functioning (Abbruzzese, Bellodi, Ferri, & Scarone, 1995; Aronowitz et al., 1994; Head, Bolton, & Hymas, 1989; Shin et al., 2004; Veale, Shakian, Owen, & Marks, 1996). OCD patients also have difficulty with high-level perceptual tasks, such as the Rey-Osterrieth Complex Fiture Test (RCFT) that involves encoding and then reproducing visual patterns (Savage et al., 1999). Past brain imaging studies point to functional and structural abnormalities associated with the symptomatology of OCD in the fronto-subcortical circuitry that includes the orbitofrontal cortex, the anterior cingulate cortex, the caudate nucleus, and the basal ganglia. For example, significantly higher metabolic activity has been observed in the fronto-subcortical circuitry in OCD patients. This elevated activation is thought to arise from disinhibition that, in turn, may be related to psychopathological symptoms such as the inability to control reflexive responses and to regulate social behavior (Baxter et al.,

1987, 1988; Benkelfat et al., 1990; Insel, 1992; Kang et al., 2004; Machlin et al., 1991; McGuire et al., 1994; Swedo et al., 1989).

As for perceptual impairments in OCD, little is known about performance on visual tasks in which cognitive load is minimized. Furthermore, little is known about their neural bases. However, there are prominent neural connections linking visual cortical areas with the fronto-subcortical circuitry. For example, eye movements are controlled by a part of the fronto-subcortical circuitry that includes the frontal eye field (FEF), the supplementary eye field (SEF) and the superior colliculus (SC). It is known that OCD patients have deficits in smooth-pursuit eye movements, in which the FEF and SEF are significantly involved (Clementz, Farber, Lam, & Swerdlow, 1996; Lencer et al., 2004; Sweeney, Palumbo, Halper, & Shear, 1992). The FEF and SEF are also well known to receive inputs from MT/MST. Similar to schizophrenia, there is also evidence that suggests abnormalities in the superior temporal cortex (STC) in OCD patients. Studies of the STC show that in OCD patients this structure exhibits unusually high levels of cerebral blood flow (Cottraux et al., 1996) and partial volumetric reduction (Choi et al., 2006). Therefore, it is natural to wonder whether these abnormalities might have a consequence on perceptual functioning.

As previously mentioned, impaired biological motion perception is not restricted to schizophrenia, but is observed in children with autism (Blake et al., 2003). Both schizophrenia and autism are associated with abnormal neural circuitry that includes the superior temporal and orbitofrontal cortices (Baron-Cohen et al., 2000; Shenton et al., 1992), which are also implicated in OCD. There are still more similarities among autism, schizophrenia and OCD. For example, individuals with autism often show increased

obsessive and compulsive behaviors (Hollander et al., 2003; Russell, Mataix-Cols, Anson, & Murphy, 2005). Likewise, more than a third of individuals with schizophrenia experience clinically significant obsessive or compulsive symptomatology (Berman et al., 1995; Bland et al., 1987; Lysaker et al., 2004). A recent study reported that OCD patients with schizotypal personality and schizophrenia patients are equally impaired in neurocognitive functions (Shin et al., 2008). Furthermore, OCD is also characterized by poor social skills (Bystritsky et al., 2001), which last even after the completion of symptom-focused treatment (Bystritsky et al., 1999; Hollander et al., 1996). Considered together, it is worthwhile to investigate biological motion perception in OCD patients as well as their ability to process coherent, translational motion, both of which are impaired in autism and schizophrenia. Finding deficits, if any, in visual motion perception in OCD will be meaningful in that it will aid to the understanding of a common dysfunction in perceptual processing among major mental disorders.

Two biological motion tasks used with schizophrenia patients were employed in this study: the biological motion discrimination task (used in experiment 1) and the detection task (used in experiment 2). Aside from the perception of biological motion, there have been no reports on visual sensitivity to simple, translational motion (global motion) in OCD patients, while schizophrenia patients are known to have deficient perception of these types of stimuli (e.g. Chen et al., 2003b). Therefore, OCD patients' ability to perceive global motion was assessed using stimuli of random-dot cinematograms (RDC) (Newsome et al., 1989). In addition to the RDC and biological motion tasks, I also included in a test battery of another global form task used in experiment 1. To reiterate, this task assessed detection of visual shape defined by a set of unconnected contours

appearing within a larger field of similar-sized contours unrelated to the shape of the target object (Kovacs and Julesz, 1993; see also Fig. 3). Therefore, this task was a good control task for both biological and global motion tasks, in that it also requires integration of spatially distributed local features but does not require motion processing.

Methods

Participants

Before the experiment, participants were screened with the same exclusion criteria, including current substance use, brain injury, any neurological disorder, and mental retardation. Twenty outpatients (8 females and 12 males) were recruited from the Seoul National University Hospital Obsessive-Compulsive Disorder Clinic in Seoul, Korea. All patients met the DSM-IV (American Psychiatric Association, 1994) criteria for OCD. Eighteen out of 20 patients were taking medication at the time of testing: sertraline (n = 4, 175mg/day), citalopram (n = 6, 40mg/day), fluoxetine (n = 5, 52mg/day), fluvozamine (n = 2, 200mg/day), risperidone (n = 5, 0.8mg/day), olanzapine, (n = 1, 10mg/day), clonazepam (n = 14, 0.7mg), valproic acid (n = 1, 375mg/day), and lamotrigine (n = 1, 50mg/day). The severity of obsessive-compulsive symptoms was assessed with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989a,b). Mean Y-BOCS score of the patients was 22.4 (SD = 9.1), which indicates a 'moderate' level of severity. Mean age was 24.3 (SD = 6.2) and mean education level was 13.9 (SD = 2.1) years. Mean IQ assessed with the Korean version of the Wechsler Adult Intelligence Scale (K-WAIS) was 111.7 (SD = 11.5).

Sixteen age, education and IQ-matched healthy controls (5 females and 11 males)

were recruited from the local community. Mean age, education and IQ was 23.2 (SD = 5.8), 14.6 (1.9), and 113.9 (11.9), respectively. Any control participant was excluded if he/she had past or present DSM-IV Axis I or Axis II disorder. None of the controls were taking psychotropic medications. Zigler social competence scale scores (Zigler & Levine, 1981) were estimated from the demographic information for all participants. All participants had normal or corrected-to-normal vision and gave written informed consent. They were paid for their participation and were provided with detailed information before the experiment. The Seoul National University Institutional Review Board approved the study protocol.

Table 8. The demographic data

	Control subjects (n = 16)	OCD subjects (n = 20)	*P*
Age	23.2 (5.8) [A]	24.25 (6.2)	n.s.
Education (years)	14.6 (1.9)	13.9 (2.1)	n.s.
WASI IQ Score	113.9 (11.9)	111.8 (11.5)	n.s.
Symptom of Obsession (YBO)[B]	n/a	11.53 (5.32)	
Symptom of Compulsion (YBC)[B]	n/a	10.84 (4.63)	
Overall symptom (YBOC)[B]	n/a	22.37 (9.09)	
Handedness (L/R/Ambi)	0/16/0	0/20/0	
Zigler score	4.13 (1.96)	2.65 (0.98)	< 0.01**

[A] Mean (standard deviation)
[B] The Yale-Brown Obsessive-Compulsive Scale
OCD, obsessive-compulsive disorder
n/a, not applicable

Stimuli and procedure

All four visual tasks were presented on an external TFT-LCD monitor (19 inches, LG Electronics, Seoul, Korea) controlled by a Macintosh computer (Powerbook G4, Apple Inc., Cupertino, CA). Two tasks were controlled by Matlab© (Mathworks Inc.

Natick, MA) and the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997), and the other two tasks were run from application programs. All experiments wre conducted in a dimly lit room where the only light source was the screen at a viewing distance of 57cm. Three out of the four visual tasks were the same tasks that were used in the experiment 1 and 2, which allows almost direct comparison of performance between the two clinical groups. Two of the tasks involved tests of perception of biological motion: the task of biological motion discrimination (in experiment 1), and the task of biological motion detection (in experiment 2). The global-form task in experiment 1 was used for OCD patients to assess their ability to perceive and integrate basic, non-motion elements into global shapes, which has not been previously studied in OCD patients. In addition to the ability of global-form perception, another non-biological motion perception task that measures the ability to detect translational, coherent (global) motion was added to the test battery. Patients with schizophrenia are already known to have deficits in perceiving coherent global motion (Chen et al., 2003b; Kelemen et al., 2005;Li, 2002; Stuve et al., 1997), whereas there have been no studies on tasks of global motion perception in OCD. Although past OCD studies revealed that OCD patients have a tendency of paying too much attention to "local" than "global" features in high-level perceptual and cognitive tasks, it is unknown whether they would show impairment on the global motion task where cognitive load is minimized. The global motion perception task, therefore, is necessary to elucidate whether OCD patients have deficits in motion perception and have selective deficits coupled with a specific type of stimulus.

Task 1: Discrimination of biological motion This is the same task used for patients

with schizophrenia in experiment 1. All healthy controls and nineteen out of 20 OCD patients successfully finished this task. One remaining patient did not participate in this task for reasons of her own, but participated in the other three tasks.

To briefly reiterate, participants viewed a single, 1 s lasting motion sequence that portrayed either biological motion or scrambled biological motion in which the spatial locations and temporal phases of the 12 dots were randomized. Following each presentation, the participant pressed one of the two pre-assigned computer keys to indicate whether the given sequence depicted human motion. There was no time limit to respond. There were 100 trials, consisting of 50 biological motions trials and 50 scrambled motions trials with the order randomized for each participant. The unbiased measure of sensitivity, d', was computed by counting the number of "hits" and "false alarms", and this d' indicated performance on the discrimination task.

Task 2: Detection of biological motion The task used in experiment 2 was introduced to OCD patients. As described in Chapter III, this task used a two-alternative, temporal forced-choice procedure to assess detectability of biological motion superimposed in a number of moving noise dots. In each trial, the participants viewed two successive, 1 sec intervals that were separated by 0.5 s blank screen. In both of the intervals, a variable number of moving black dots appeared. One of the intervals had a subset of dots defined as biological motion, and in the other interval, the scrambled version of that biological motion was presented. The dots defining biological or scrambled motion appeared anywhere within 80 pixels of fixation to make it impossible for the participants to monitor a small fixed region. The participant indicated which of the two intervals

contained biological animations by pressing a key, guessing if necessary. The difficulty of the task varied by changing the number of noise dots according to a two-up/one-down staircase rule, which was automatically terminated after 16 reversals in the staircase, and the average number of noise dots over the last six reversals was calculated as the threshold, or an index of performance.

Task 3: Detection of coherent, translational motion This task measured the detectability of weak, translational motion within a field of dynamic noise dots, and is a widely used task in studies of motion perception (Braddick et al., 2001; Chen et al., 2003b; Hiris & Blake, 1995; Newsome et al., 1989; Rizzo & Nawrot, 1998; Wattam-Bell, 1994). The task in the current experiment used a two-alternative, spatial forced-choice procedure wherein two stimulus alternatives are presented simultaneously (Fig. 25).

On each trial, two arrays of moving dots (black dots against a white background) were presented on either side of a central fixation point. Each array of dots comprised a virtual region the diameter of which was 6 ° visual angle. The nearest borders of the two arrays were separated by 3 ° on either side of the fixation point. Each of the two arrays consisted of 100 dots, and all dots had the same size (3 arc-min) and moved at the same speed of 1.2 °/sec. Dots in one of the two arrays moved entirely randomly with respect to direction, whereas dots in the other array consisted of noise dots and a variable percentage of signal dots that coherently moved upward. The location of the array with signal dots was randomly determined over trials. The participant's task was to indicate, by key press, which dot array contained signal dots (coherent motion), guessing if necessary. The percentage of signal dots was varied over trials according to a two-up /

one-down staircase procedure, which started with 50% signal dots. The staircase was terminated after 10 reversals in the direction of the staircase, and the average percentage of coherent signal dots over the last four reversals was calculated as the estimate of threshold.

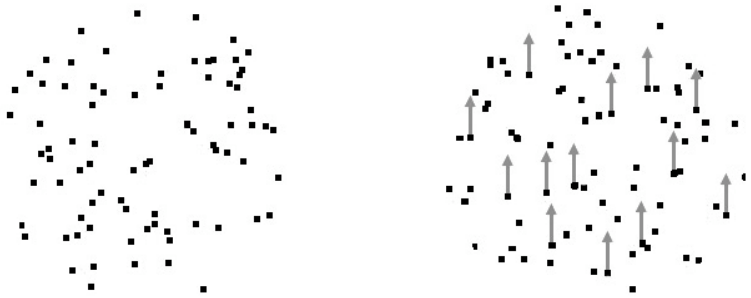

Figure 25. Coherent, global motion task. One of the two displays has a group of dots moving coherently upward while the others and all dots in the other display moved entirely randomly.

Task 4: Global form perception This task was the same four-alternative, forced-choice task used in experiment 1, which measures the ability to group small, stationary line elements into a larger, global form. The screen was divided into four equal-sized quadrants and was filled with short lines, most of which were oriented randomly. In one of the four quadrants, a small group of six lines formed a quasi-circular shape within a randomly selected region of the quadrant, and the participant's task was to indicate the quadrant by pressing one of four spatially matched computer keys. Task difficulty was adjusted by "jitter" in the orientation of each line forming the shape trial-by trial, according to a one-up/one-down staircase procedure. There were 100 trials, and the mean of the jitter from the last eight trials of the staircase provided the estimate of the jitter threshold.

Results

Task 1: Discrimination of biological motion from non-biological motion Mean sensitivity of discrimination (d') from OCD and healthy controls are shown in Fig. 26A. Mean d' was 2.09 (SE = 0.14) in OCD patients and 2.54 (SE = 0.13) in healthy controls. This difference was statistically significant (t (33) = 2.21, $p < 0.05$). As in patients with schizophrenia, OCD patients also performed poorer on the biological motion discrimination task compared to healthy people. False alarm rates were comparable between groups. However, OCD patients showed a lower hit rate than controls, and the difference was close to significance (t (33) = 1.99, $p = 0.055$) with medium-to-large effect size (Cohen's $d = 0.69$). Correlation between d' values and OCD symptom severity was not significant (YBO - d': r = 0.26, p = 0.30; YBC - d': r = 0.029, p = 0.91; YBOC - d': r = 0.17, p = 0.51). General social functioning estimated by Zigler scale was not correlated with d' within each group (OCD: r = -0.07, p = 0.78, control: r = -0.29, p = 0.27) and for all participants (r = 0.007, p = 0.97), although a group difference on the Zigler score was significant (t (34) = 2.94, p < 0.01).

Task 2: Detection of biological motion In the task of detecting biological motion superimposed on a number of noise dots, OCD patients also showed significantly poorer performance compared to healthy controls. Mean estimated threshold (number of noise dots) guaranteeing 71% accuracy in the OCD group was 35.05 (SE = 4.29), and it was 54.71 (SE = 4.16) in the control group (t (34) = 3.24, p < 0.005). Therefore, OCD patients showed similar deficits as schizophrenics in perceiving biological motion on both tasks of detection and discrimination. Symptoms were not significantly correlated with detection

performance (YBO: r = 0.21, p = 0.39; YBC: r =0.37, p = 0.12; YBOC: r = 0.31, p = 0.19). Zigler score was not significantly correlated with performance within each group (OCD: r = -0.23, p = 0.34; control: r = -0.19, p = 0.47) and for all participants (r = 0.07, p = 0.69), either.

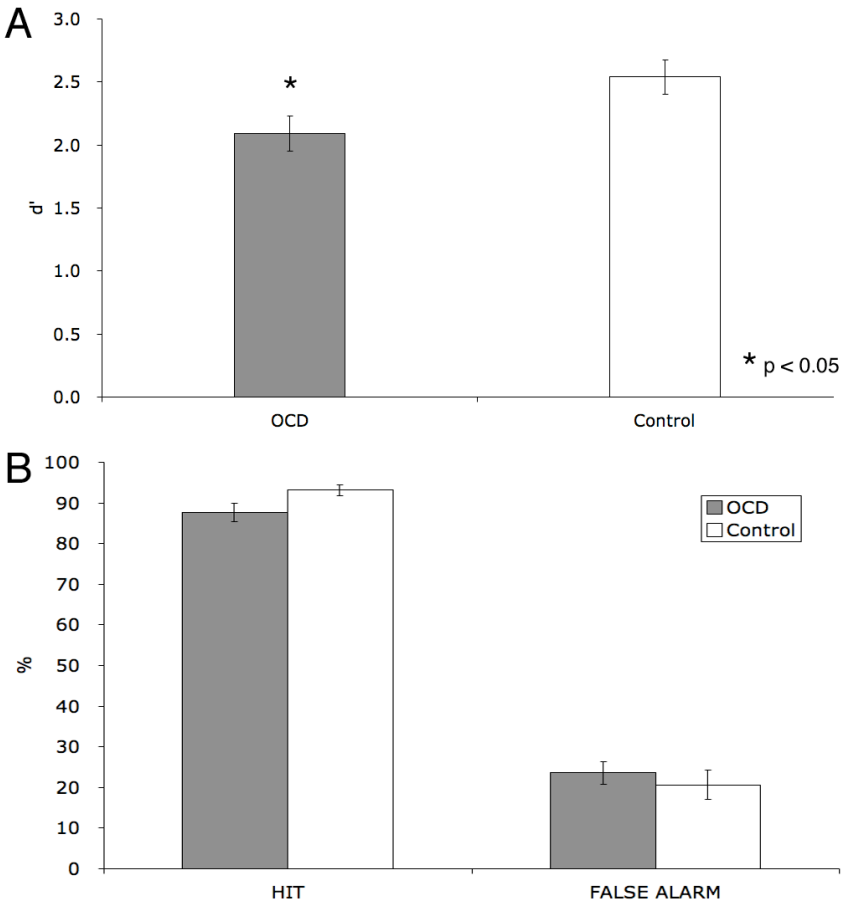

Figure 26. Performance on the biological motion discrimination task in OCD and control group. A: Mean *d'* values were significantly different between groups. B: OCD patients and controls were comparable in their false-alarm rate while OCD patients had lower hit rate compared to controls. This difference was almost significant (p = 0.055). OCD patients' lower hit rate and comparable false alarm rate is the opposite pattern compared to that observed in patients with schizophrenia.

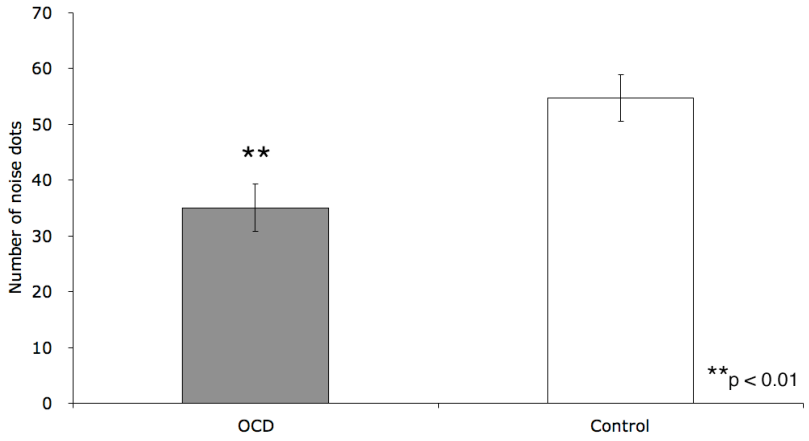

Figure 27. Performance on the biological motion detection task in OCD and control group

Task 3: Detection of coherent motion In this task, participants' were asked to detect a subset of dots moving in one, given direction among noise dots that moved in all directions. The mean threshold (i.e. minimum coherence level for 71% guaranteed detection) in OCD patients was 8.15 (SE = 1.22), and it was 9.84 (SE = 1.24) in controls. This difference was not statistically significant (t (34) = -0.96, p = 0.34). Therefore, an OCD patients' ability to detect non-biological, global motion was spared, while their ability of perceiving biological motion was impaired. I also examined whether the stimulus exposure duration possibly affected participants' performance, because motion sequences in this task were presented until participants responded. First, the difference in mean elapsed time (min) for finishing this task was not statistically significant (8.8 (SD = 5.7) in OCD and 6.7 (SD = 2.6) in controls, t (34) = 1.36, p = 0.18). Second, elapsed time was not significantly correlated with performance (r = -0.37, p = 0.11). The correlation between symptoms and elapsed time was also not significant (YBO: r = -0.08, p = 0.73; YBC: r = 0.24, p = 0.33; YBOC: r = 0.08, p = 0.77). Therefore, it is unlikely that exposure duration influenced performance on this task.

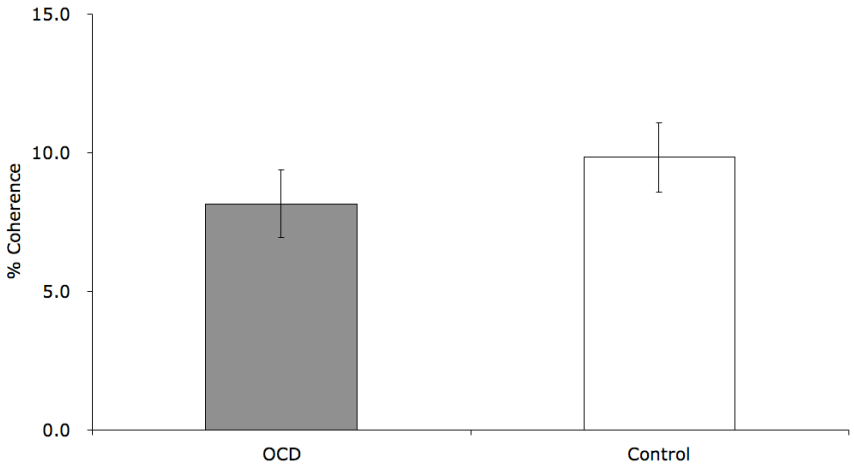

Figure 28. Mean % Coherence threshold in coherent motion detection task. OCD patients' performance was not differ from that of healthy controls.

Task 4: Global form perception To reiterate, this task involved judging in which of four possible locations a target figure that was defined by a set of spatially distributed contours appeared with variable jittering of the target contours over trials. The mean (SE) jitter threshold values in the two groups were equivalent as shown in Fig. 29; it was 23.05 (SE = 0.89) in OCD and 23.18 (SE = 1.27) in controls ($t(34) = 0.089$, $p = 0.93$). Elapsed time for completing the task was not different between groups ($t(34) = 0.82$, $p = 0.42$). The jitter threshold and elapsed time were not correlated with symptoms.

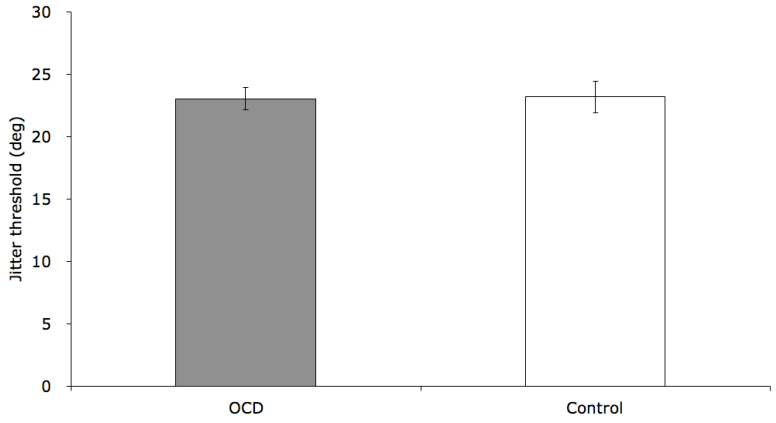

Figure 29. Mean jitter threshold (deg) in global form perception task. Performance in the two groups was almost equivalent.

Discussion

This is the first study to explore whether people with OCD have deficits in visual perception, in particular biological motion perception. The results showed that OCD patients, relative to normal controls, experienced difficulty in perceiving PL animations portraying the kinematics of human activity, while their ability to perceive non-biological global motion and static global form was comparable to that of healthy controls. Impaired biological motion perception in OCD is a new finding as it was in schizophrenia. However, unlike schizophrenia, OCD patients show intact perception of coherent, translational motion signals.

Before discussing the implications of these findings, it is necessary to consider possible alternative, non-perceptual accounts of this selective deficit in biological motion perception. First, like patients with schizophrenia in experiments 1~ 4, most of the OCD patients in this study were medicated, and the possible effects of medication on biological motion perception is unknown. In the case of schizophrenia, psychotropic medications do not seem to affect perceptual and cognitive abilities in any specific manner (Allen et al.,

1997; see also Chen et al., 2003a). In experiment 1, performance of schizophrenic patients was not correlated with the dosage of antipsychotic medication. Although a specific pharmacological effect on visual perception in OCD is unknown, it seems unlikely that medication in these patients would produce such specific deficits on biological motion perception only but not on coherence detection or shape recognition. Another issue is about the cognitive functioning of OCD patients. Several earlier studies reported that patients with this disorder exhibit a "local-bias" in the allocation of attention during cognitive tasks such as the Rey-Osterrieth Complex Figure Test (Savage et al., 1999). Therefore, one may ask whether such a "local-bias" would also affect OCD patients' perception of biological motion, perhaps because they focused on individual dots and not on the spatiotemporal pattern among dots. This is unlikely because in the other two tasks, coherent motion detection and global form perception, OCD patients performed normally. These non-biological motion tasks also require integration of local elements distributed over space and embedded in noise elements. The biological motion discrimination task had no noise dots, but OCD patients performed poorly on this task. Furthermore, as suggested in the past lesion studies and imaging studies (Battelli et al., 2003; McLeod et al., 1996; Schenk & Zihl, 1997a,b; Thompson et al., 2005; Vaina et al., 1990), biological motion perception may require a different kind of global perception that precedes processing of local elements, rather than the simple integration of local elements into a global shape. The results from experiments 1~ 4 with also suggest that biological motion perception is processed differently from general coherent motion perception. As with schizophrenia, the correlations between performance on either of the biological

motion tasks and clinical symptoms (YBOC scores) were not significant, suggesting that symptom severity does not predict the extent of perceptual deficit.

OCD patients' normal performance on the global form task, in which spatial integration of stationary line elements is required, indicates that the primary visual area (V1) is intact in these patients by the same reason discussed in experiment 1. To reiterate, area V1 is widely believed to contain neural interconnections among orientation-selective neurons subserving integration of contour information in targets (Gilbert, 1993). Area V1 also contains movement (direction) sensitive neurons (e.g. Movshon & Newsome, 1996). However, those neurons do not have selective response to distinguish biological motion from non-biological motion.

As also discussed in the previous experiments on schizophrenia, motion-sensitive areas MT and MST do not seem to be responsible for impaired biological motion perception. Although past OCD studies that reported abnormal smooth-pursuit eye movements (SPEM) implicated area MT, a recent study suggested that this impaired SPEM is not correlated with motion perception in OCD (Lencer et al., 2004). Furthermore, comparable performance of OCD patients on the coherent motion detection task in this study strongly suggests that area MT is functional in motion perception. This result provides another piece of evidence suggesting dissociated processing between biological motion and coherent motion, in addition to the results from past lesion case and psychophysical studies (Battelli et al., 2003; McLeod et al., 1996; Shenck and Zihl, 1997a,b; Thornton et al., 2002; Vaina et al., 1990). Therefore, it is tempting to speculate that deficient biological motion perception observed in OCD patients may be traced to dysfunction within the STS and its surrounding regions like in the patients with

schizophrenia. In fact, there are earlier physiological and anatomical studies of OCD patients that reported abnormally higher regional cerebral blood flow levels (Cottraux et al., 1996) and partial volumetric reduction within areas along the superior temporal gyrus (STG) (Choi et al., 2006), implicating possible dysfunction of the STC. However, it remains unclear whether those brain abnormalities are really associated and, if so, how they are associated with impaired biological motion perception. Future studies should be conducted to pursue this particular question.

Another interesting difference in performance between patients with OCD and schizophrenia is that OCD patients' significantly lower *d′* value is ascribed to their lower *hit* rates, rather than higher false alarm rates. In other words, OCD patients had similar *d′* value to those of schizophrenia patients, but the underlying response pattern was different. The reason why OCD and schizophrenia patients have different ways for discriminating biological motion is unclear. One possibility that can easily come to mind is that OCD patients may have difficulty perceiving biological motion signal itself, whereas patients with schizophrenia seem to have abnormal function of filtering out irrelevant (scrambled) motion signals. Additional functional imaging studies will enable researchers to find the underlying neural differences between the two groups. Another possibility is that OCD patients may have responded in a more conservative way than normal controls during the discrimination task because of their symptom of obsession. However, a significant correlation between symptom of obsession and *d′* values or hit-rates was not observed.

To close, children with autism and adults with schizophrenia both show deficits in tasks that tap ToM, which is related to social functioning (also note that schizophrenia

patients in experiment 1~ 4 scored significantly lower in the Eyes Task). The neural network that putatively supports ToM includes the amygdala, STS, and the orbitofrontal cortex (Baron-Cohen et al., 2000). Thus, abnormal functioning of the STS and its surrounding regions involved in biological motion perception may co-occur with deficits of ToM (and possibly impaired general social functioning). Indeed, this possible co-occurrence was consistently suggested by the results from experiment 1 to 4. The limitation of the current experiment is that OCD patients' ability of ToM or general social functioning was not measured. Therefore, a next logical step, in addition to a follow-up imaging study, would be to test the relationship between biological motion perception and social functioning in OCD patients.

CHAPTER VI

CONCLUSION

Visual deficits and impaired social functioning have been extensively studied as core features that characterize schizophrenia, in addition to a wide range of cognitive impairments. However, perception of socially-relevant motion signals have not been studied in schizophrenia or in obsessive-compulsive disorder. The major goal of this dissertation was to explore whether patients with schizophrenia and OCD have difficulty in processing socially meaningful motion stimuli (biological motion), and to further reveal the nature of the deficit in biological motion perception. The first behavioral study described in CHAPTER III documented the deficit in biological motion perception in patients with schizophrenia, which had not been reported in the scientific literature previously. A series of behavioral studies successfully provided additional evidence for impaired biological motion perception in schizophrenia and established that it is reliably observed regardless of task demands. The fMRI study was built upon the behavioral experimental data and provided further evidence for impaired biological motion perception in schizophrenia patients. The fMRI study also yielded interesting results that could further elucidate the mechanisms of biological motion perception in healthy people. In CHAPTER V, a series of behavioral experiments on visual perception including biological motion tasks were conducted to document visual deficits in patients with OCD as a comparison group to schizophrenic patients. The purpose of this study was to observe whether OCD patients would have an impairment in biological motion

perception similar to that reported in schizophrenia patients. The results revealed the novel finding that OCD patients have deficits in perceiving biological motion, and that this deficit is even more specific compared to that of schizophrenia patients who also have impaired coherent, global motion perception. Investigation into association between biological motion perception and social functioning suggested the possible co-occurrence of these two kinds of impairments, thereby implicating that impaired biological motion could be a behavioral marker for degraded social functioning.

The studies on schizophrenia patients in this dissertation lead to interesting speculations about the nature of the deficit in biological motion perception. At first, it was hypothesized that schizophrenia patients have difficulty perceiving biological motion because of impaired processing of the hierarchical, pendular motions characterizing biological motion. In fact, patients had lower sensitivity in discriminating (experiment 1), and detecting (experiment 2) biological motion, and lower accuracy in fine discrimination of partially scrambled biological motions (experiment 3). However, these results could be attributed to patients' tendency of judging scrambled motion as biological motion rather than a failure to process unique features of biological motion. In other words, although schizophrenia patients exhibited impaired biological motion perception as hypothesized, the nature of the deficit was somewhat unexpected. They may have failed to attenuate or filter out irrelevant stimuli (i.e. non-biological motion) rather than having failed to process relevant stimuli in general terms. This failure also could account for other kinds of early sensory deficits (e.g. Braff et al., 1992; Green et al., 1994b), oculomotor response (Winograd-Gurvich, Fitzgerald, Georgiou-Karistianis, Millist, & White, 2008) or higher-level cognitive disinhibition (e.g. Barch et al., 2001). Indeed, the results from

the fMRI experiment strongly support this speculation: schizophrenia patients showed STSp activation to biological motion as strong as that of healthy controls, but also showed even stronger activation to scrambled motion. On the other hand, healthy controls exhibited a clear activation difference when they viewed biological and scrambled motions, indicating that patients' poor biological motion perception is associated with their hyperactivation to non-biological motion within the STSp region that is selectively responsive to biological motion in the normal brain.

Imaging results from normal controls yielded a novel finding concerning the nature of normal biological motion perception. Control participants' strong STSp activation to biological motion but not to scrambled motion dovetails nicely with the results of past imaging studies (e.g. Grossman et al., 2000). Interestingly, they exhibited strong STSp activation when they judged a scrambled motion as biological and this activation was just as strong as when they viewed pure biological motion. In other words, false-alarms resulted in strong STSp activation. Even when an ambiguous stimulus (i.e. 37% scrambled biological motion) was presented, STSp was strongly activated if the observer perceived it as biological motion, which was not an observed phenomenon in schizophrenia patients. These results indicate that activation within this region may be modulated by an observer's subjective perception, whatever the actual stimulus was. Previous studies have demonstrated that visual discrimination of a human agent is enhanced by meaningfulness of the biological motion (Neri, Luu, & Levi, 2006), and STSp activation to the same physical stimuli can be changed dependent on training (Grossman et al., 2004). The STSp region may be involved in processing movement characteristics that characterize living beings, rather than responding to the presence of

living beings (Schultz, Friston, O'Doherty, Wolpert, & Frith, 2005). For example, interaction between the movements of two abstract objects can enhance STSp activation (Schultz et al., 2005). In addition, the results in this dissertation suggest an important clue that may help elucidate the neural mechanism: the STSp region is selectively responsive to the "internally represented" visual percept of biological motion, in addition to simple physical characteristics induced by the motion of geometrical shapes. Similar to the current results, it was reported that STSp could be activated if biological motions were imagined without their actual presentation by trained observers (Grossman & Blake, 2001). Considered together, all of these results strongly suggest that higher-level or top-down processing plays a crucial role in the perception of biological motion, in addition to the argument emphasizing an automatic perception based on a low-level or bottom-up processing in earlier works (e.g. Johansson, 1973; Mather et al., 1992). In this context, the inappropriately generated internal representation of biological motion may account for impaired biological motion perception in schizophrenia patients.

Another important finding is that of activation within the motion-sensitive area MT in schizophrenia patients. Their weaker MT activation to PL animations, regardless of biological or scrambled motion, provided physiological evidence that supports past psychophysical research which suggests an association between MT dysfunction and poor perception of global motion stimuli. It is evident that PL animations belong to global motions if motions are simply categorized into local and global types. More importantly, investigation into the correlation between MT and STSp activations indicated that patients' impaired biological motion perception did not originate from their poor ability to perceive general motion (e.g. Chen et al., 2003b), which was a

controversial issue throughout the behavioral experiments. In addition, the absence of this correlation in healthy controls also confirmed that the neural events critical for perception of coherent motion differ from those involved in biological motion perception (Blake & Shiffrar, 2007, Sekuler et al., 2002).

Impaired perception of biological motion in OCD patients is also a meaningful finding in that it was identified for the first time, similar to schizophrenia. Their specific deficit in perception of biological motion, but not in coherent motion, further confirms that the visual mechanisms for processing general motion and biological motion can be dissociated. However, the results suggested that the nature of the deficit could be different from that of schizophrenia patients; OCD patients might have failed to process characteristics of movement depicting human activities, rather than inappropriate perception of non-biological, scrambled motion. Future studies using functional imaging are needed to elucidate this issue clearly.

Lastly, there are limitations and caveats. First, most patients with schizophrenia and OCD who participated in the studies had been taking psychotropic medications for a long time, including at the time of testing. Previous studies reported that medications do not seem to affect perceptual and cognitive abilities in any specific way (Allen et al., 1997; see also Chen et al., 2003a). Lack of a correlation between medication and performance on the task of biological motion discrimination (experiment 1) also suggests that the specific deficits in biological motion perception in schizophrenia and OCD are not associated with the effect of psychotropic drugs. Even if, however, the effects of antipsychotic medication on perceptual abilities are peripheral, it is still necessary to be mindful of the potential long-term consequence of administration. Future studies with

medication-free participants will be needed to clarify this controversy. Second, it was not investigated precisely whether specific clinical symptoms associated with visual experiences would be related to impaired biological motion perception in the patients groups. Overall symptoms were not correlated with performance on the visual tasks in both schizophrenia and OCD patients, indicating that the observed deficit in this dissertation is not a simple by-product of clinical symptoms. However, it will be necessary to examine even further whether correlations with clinical subscale scores exist. This was impossible to perform in this dissertation because of the sparse distribution of subscale scores for a restricted number of participants. Third, although the correlations between biological motion perception and social functioning (Zigler score and Eyes task score) suggested that worse performance might be one possible behavioral manifestation of impaired social functioning in schizophrenia, the interpretation is limited because more precise assessment of social functioning is required. Zigler scale score was merely an estimate based on demographic information, implicating global social functioning, and the Eyes task focused on one aspect of social functioning, ToM. Therefore, it is still unclear how biological motion perception deficit is related to one's social functioning in a specific manner. A more precise assessment of social functioning is needed in future studies. Since social functioning of OCD patients were estimated with the Zigler scale only, the possible relationship between OCD patients' deficits in biological motion perception and their social functioning should be further investigated in future studies.

In conclusion, while there are caveats, the results reported here clearly indicate that both the patients with schizophrenia and OCD do have specific impairment in perception

of biological motion, which is not necessarily coupled with general motion perception. Results from the functional imaging study were consistent with the behavioral results from schizophrenia patients and healthy controls. Furthermore, healthy controls' performance and brain activation in error trials and trials with ambiguous stimuli revealed a new aspect of perception of biological motion in the normal brain. All of the results implicated strong involvement of top-down processing in biological motion perception. These findings could provide a new perspective for future research such as research on a further definitive neural mechanism accounting for STSp activation to subjectively perceived biological motion in healthy individuals. Further research is needed on a more precise relationship between impaired biological motion perception and social dysfunction in schizophrenia, as well as, in OCD. Finally, further research is needed on elucidating the neural interconnection among brain regions forming the "social-brain", and on neural activities underlying impaired biological motion perception in OCD.

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