NeuroImage: Clinical 9 (2015) 233–243

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Abnormalities in personal space and parietal–frontal function in schizophrenia

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ARTICLE INFO

Article history:
Received 24 April 2015
Accepted 15 July 2015
Available online 6 August 2015

Keywords:
Schizophrenia
Personal space
Faces
Object processing
Parietal cortex
Premotor cortex

ABSTRACT

Schizophrenia is associated with subtle abnormalities in day-to-day social behaviors, including a tendency in some patients to "keep their distance" from others in physical space. The neural basis of this abnormality, and related changes in social functioning, is unknown. Here we examined, in schizophrenic patients and healthy control subjects, the functioning of a parietal–frontal network involved in monitoring the space immediately surrounding the body ("personal space"). Using fMRI, we found that one region of this network, the dorsal intraparietal sulcus (DIPS), was hyper-responsive in schizophrenic patients to face stimuli appearing to move towards the subjects, intruding into personal space. This hyper-responsivity was predicted both by the size of personal space (which was abnormally elevated in the schizophrenia group) and the severity of negative symptoms. In contrast, in a second study, the activity of two lower-level visual areas that send information to DIPS (the fusiform face area and middle temporal area) was normal in schizophrenia. Together, these findings suggest that changes in parietal–frontal networks that support the sensory-guided initiation of behavior, including actions occurring in the space surrounding the body, contribute to social dysfunction and negative symptoms in schizophrenia.

1. Introduction

It has been found in a number of studies that abnormalities in social perception are predictive of levels of everyday functioning in schizophrenia (Couture et al., 2006; Green et al., 2012; Hooker and Park, 2002; Mancuso et al., 2011; Rassovsky et al., 2011). Other work indicates that impairments in social functioning may precede and predict the development of schizophrenia in those at risk (Alderman et al., 2014; Cannon et al., 2008; Kwapil, 1998). Thus, abnormalities in processing social information may represent a candidate target for early intervention efforts. However, the neurobiological mechanisms underlying these impairments are poorly understood.

Previously, social perception and cognition have been typically measured in schizophrenia using affect recognition, mentalization or social inferencing paradigms (Green and Leitman, 2008; Pinkham, 2014). These processes are at least partly dependent on semantic or real-world knowledge (e.g., of emotion labels or common social situations), which can be impaired in individuals with schizophrenia as a consequence of their illness. Given this, experimental paradigms that measure low-level, non-verbal processes involved in social behavior are needed (Green et al., 2013).

One such non-verbal process is social spacing, i.e. "personal space". Personal space is the "comfort zone," or preferred distance, that one individual maintains from another nearby person (Hayduk, 1983). Like eye gaze and facial expressions, personal space plays an important role in social communication. For example, greater physical proximity during social interactions promotes cooperation and affiliation (Collett, 1971; Kahn and McGaughey, 1977), whereas greater distances between people guard against physical threats and can convey mistrust (Dosey and Meisels, 1969; Graziano and Cooke, 2006; Lourenco et al., 2011). Although personal space is influenced by a number of variables, including familiarity, social status and cultural factors (Hayduk, 1983), there is also evidence for an "optimal distance" for individuals that stabilizes during adolescence (Bar-Haim et al., 2002; Hayduk, 1983).

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http://dx.doi.org/10.1016/j.nicl.2015.07.008

Findings of enlarged or inflexible personal space have been consistently reported in schizophrenia (Deus and Jokic-Begic, 2006; Duke and Mullens, 1973; Horowitz et al., 1964; Nechamkin et al., 2003; Park et al., 2009; Srivastava and Mandal, 1990). In some studies, personal space abnormalities have been linked specifically to negative symptoms, which can include impairments in social behavior, such as social withdrawal (Nechamkin et al., 2003; Park et al., 2009). However, the cognitive or neural basis of these behavioral abnormalities is not known. One possibility, which we sought to investigate in the current study, is that the functioning of the parietal and frontal regions involved in monitoring and generating actions within the space near the body ("near space") in primates (Brozzoli et al., 2011; Colby et al., 1993; Fogassi et al., 1996; Graziano et al., 1997; Sereno and Huang, 2006) is altered in patients with schizophrenia.

Although the neural mechanisms responsible for social spacing-related behaviors are incompletely understood, we recently found evidence that the near space-monitoring network in humans is 1) particularly sensitive to social information and 2) appears to influence personal space. In an fMRI study of 21 healthy subjects, we showed that two primary nodes of the near space-monitoring network, the dorsal intraparietal sulcus (DIPS) and the ventral premotor area (PMv), were preferentially responsive to images of human faces (i.e., social stimuli) that appeared to approach or "loom" towards (versus withdraw from) subjects (Holt et al., 2014). This approach-biased activity did not occur in response to non-social stimuli. This network also showed stronger resting-state functional coupling in individuals who preferred physical proximity to others, compared to those who preferred greater social distance, suggesting that it may play a role in determining personal space characteristics and perhaps related social behaviors.

Therefore, based on this prior work, in the current investigation we sought to test whether the function of this parietal–frontal network is (1) altered and (2) predictive of abnormalities in personal space in schizophrenia. Also, since abnormalities in schizophrenia in lower-level visual areas (Javitt, 2009), such as those dedicated to face perception or motion processing, could theoretically influence the function of this near space–monitoring sensory–motor pathway, in another cohort of schizophrenic patients and demographically-matched healthy subjects, we conducted additional control experiments measuring the function of lower-level visual areas in schizophrenia.

2. Materials and methods

2.1. Study 1: participants

For all subjects, the exclusion criteria included severe medical illness, significant head trauma, neurologic illness, substance abuse during the past 6 months and contraindications for MRI scanning (e.g., implanted metal objects, claustrophobia).

Healthy subjects were recruited via advertisement and screened for psychiatric illness using the Structured Clinical Interviewfor DSM-IV (SCID) (First et al., 1995); subjects with past or present psychiatric diagnoses were excluded from this group. Patients who met the DSM-IV criteria for schizophrenia according to the SCID were recruited and characterized by the Massachusetts General Hospital (MGH) Schizophrenia Program. The schizophrenia (n = 15) and control (n = 14, a subgroup of the Holt et al., 2014 cohort) groups were matched with respect to age, mean parental education and socioeconomic status, (see Table 1A). One additional healthy control was included in the functional connectivity analysis; the schizophrenia and control groups remained matched for demographic characteristics with this additional subject. Written informed consent was obtained from all subjects prior to enrollment in accordance with the guidelines of the Partners HealthCare Institutional Review Board. Levels of positive and negative symptoms were evaluated in each schizophrenic patient by one trained rater (DJH) using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) on the day of scanning.

Table 1
Demographic information about the subjects.

	Control (n = 14)		Schizophrenia (n = 15)		P-Value
	Mean	SD	Mean	SD	
A. Study 1: personal space and parietal–frontal function					
Age(years)	26.0	6.5	30.1	9.1	0.18
Premorbid IQ[a]	112.2	4.8	108.9	6.8	0.15
Parental education (years)	14.9	2.1	14.8	3.1	0.97
PANSS Total			52.3	12.0	
PANSS Positive Symptoms Subscale			13.9	5.2	
PANSS Negative Symptoms Subscale			12.9	5.2	
PANSS General Symptoms Subscale			25.5	4.7	
Duration of illness (years)			9.9	8.3	
Antipsychotic dose in chlorpromazine equivalents (n = 7)			430.7	354.7	
B. Study 2: lower-level face and motion processing					
Age(years)	40.7	14.4	41.3	11.4	0.9
Premorbid IQ[a]	113.7	6.1	103.4	9.7	0.001
Parental education (years)	13.1	2.8	13.4	1.7	0.64
PANSS Total			47.5	10.3	
PANSS Positive Symptoms Subscale			12.0	4.5	
PANSS Negative Symptoms Subscale			12.5	4.6	
PANSS General Symptoms Subscale			23.1	4.8	
Duration of illness (years)			18.42	12.87	
Antipsychotic dose in chlorpromazine equivalents (n = 17)			542.29	479.35	

Demographic and clinical information about the subjects of Study 1 (A) and Study 2 (B) are listed. In Study 2, the cohort was older and the patients were more likely to be treated with antipsychotic medication, compared to Study 1. Also, p-values of independent Student's t-tests comparing the two groups on key demographic variables (age, premorbid IQ or parental education) are included.

[a] Measured using the North American Adult Reading Test. PANSS, Positive and Negative Syndrome Scale.

2.2. Study 1: MRI data acquisition

All MRI data were collected on a 3 T Siemens Tim Trio scanner(Iselin, NJ). Two anatomical 3D MPRAGE scans were collected for each participant (TR = 2530 ms, TE = 3.39 ms, flip angle = 7°; 256 coronal slices, spatial resolution 3 mm isotropic voxels). 10 functional runs were collected (TR = 2000 ms, TE = 30 ms, flip angle = 90°; 33 axial slices; 3 mm isotropic voxels). In addition, one 6-min-20-s resting BOLD scan (TR = 5000 ms; TE = 30 ms; flip angle = 90°; 55 axial slices, 76 images per slice, 2 mm isotropic voxels) was acquired, during which subjects were instructed to keep their eyes open and blink normally.

2.3. Study 1: stimuli

During each functional run, subjects viewed stimuli that appeared to either approach or withdraw from the subject (i.e., expand or contract in size) (Holt et al., 2014), Stimuli were images of human faces (3 males and 3 females, with neutral facial expressions) or cars. Each of the four conditions of interest (i.e., Face Approach, Face Withdrawal, Car Approach, Car Withdrawal) was presented in a block of 16 s duration (Fig. 1A). Two 16-s fixation blocks were presented at the beginning and end of each run. In each run, subjects viewed two blocks of each of the four conditions, randomly presented. The minimum stimulus size was 120 × 120 pixels and the maximum stimulus size was 43,239 × 43,239 pixels. The stimuli changed in size, appearing to approach or withdraw from the subject, at a rate equivalent to a speed of 112 cm/s — a typical speed for walking. The face stimuli were created with FaceGen (http://www.facegen.com), a program used to create realistic human faces. The car stimuli were constructed from photographs of cars.