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An exploratory study of the relationship between neurological soft signs and theory of mind deficits in schizophrenia

Stefano Romeo, Alessio Chiandetti, Alberto Siracusano, Alfonso Troisi *

Department of Systems Medicine, University of Rome Tor Vergata, via Nomentana 1362, 00137 Rome, Italy

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A B S T R A C T

Indirect evidence suggests partially common pathogenetic mechanisms for Neurological Soft Signs (NSS), neurocognition, and social cognition in schizophrenia. However, the possible association between NSS and mentalizing impairments has not yet been examined. In the present study, we assessed the ability to attribute mental states to others in patients with schizophrenia and predicted that the presence of theory of mind deficits would be significantly related to NSS. Participants were 90 clinically stable patients with a DSM-IV diagnosis of schizophrenia. NSS were assessed using the Neurological Evaluation Scale (NES). Theory of mind deficits were assessed using short verbal stories designed to measure false belief understanding. The findings of the study confirmed our hypothesis. Impaired sequencing of complex motor acts was the only neurological abnormality correlated with theory of mind deficits. By contrast, sensory integration, motor coordination and the NES Others subscale had no association with patients' ability to pass first- or second-order false belief tasks. If confirmed by future studies, the current findings provide the first preliminary evidence for the claim that specific NSS and theory of mind deficits may reflect overlapping neural substrates.

1. Introduction

Neurological soft signs (NSS) refer to subtle neurological abnormalities in motor coordination, sensory integration, and sequencing of complex motor acts (Heinrichs and Buchanan, 1988). Numerous studies over the past 40 years have shown that patients with schizophrenia have more soft signs than healthy controls and patients with other psychiatric diagnoses, although the prevalence of NSS in some mental disorders (e.g., bipolar disorder and pervasive developmental disorders) is equal to or higher than that observed in schizophrenia (Halayem et al., 2010; Zhao et al., 2013b). Prevalence rates for NSS in schizophrenia range from 50% to 73%, compared with only 5% in controls. Family members of schizophrenia patients also manifest higher rates of NSS (Compton et al., 2007). Several features of NSS suggest that these neurological abnormalities can be conceptualized as a vulnerability marker for schizophrenia, and may represent a useful phenotype in genetic studies (Chan and Gottesman, 2008; Chan et al., 2010). Typical soft signs have been demonstrated in patients with schizophrenia in different stages of the illness, including individuals at risk for psychosis (Barkus et al., 2006), patients in the first-onset medication naïve stage (Zabala et al., 2006) as well as patients in the chronic stage (Buchanan and Heinrichs, 1989; Chan and Chen, 2007). In addition, NSS have also been shown to be relatively stable across time without significant impact from medications (Chen et al., 2005; Scheffer, 2004).

In classical definition, NSS are described as a group of non-localizable neurological abnormalities that are considered to reflect diffuse brain structural changes. However, many recent studies using magnetic resonance imaging (MRI) have identified localized cerebral changes associated with NSS, including dorsolateral and medial prefrontal cortices, lateral temporal, occipital, superior parietal, and medial parieto-occipital cortices (Gay et al., 2013; Kong et al., 2012). In their recent meta-analysis of structural and functional MRI studies, Zhao et al. (2013a) reported that NSS were associated with atrophy of the precentral gyrus, the cerebellum, the inferior frontal gyrus, and the thalamus and with altered brain activation in the inferior frontal gyrus, bilateral putamen, the cerebellum, and the superior temporal gyrus. The involvement of cortical regions in the pathogenesis of NSS may explain their relationships to neurocognitive functions in schizophrenia.

Patients with greater number of NSS show impairments in different neurocognitive functions, including executive attention, logical memory, and visual reproduction (Dazzan et al., 2008; Chan et al., 2009). In a recent meta-analysis of published studies reporting clinical correlates of NSS, Chan et al. (2010) found that

* Corresponding author. Tel.: +39 06 41400356.
E-mail address: alfonso.troisi@uniroma2.it (A. Troisi).

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cognitive and NSS data share approximately 10% of their variance, implying that these data reflect associated, but distinct, aspects of neurobehavioral function in schizophrenia. Specific relationships were found between sensory and motor soft signs and several aspects of cognitive ability including spatial, executive, and language performance. Sensory integration signs were significantly related to IQ measures whereas motor system dysfunctions were associated with disturbances in systems underlying spatial and executive processes.

Among patients with schizophrenia spectrum disorders, neurocognition is also partially correlated with those neuropsychological functions that have been collectively subsumed under the term of social cognition (Fanning et al., 2012), i.e. the mental processes of perceiving, interpreting, and responding to social information (Lieberman, 2007). Many patients with schizophrenia have profound difficulties in inferring the mental states of other individuals. According to prevailing clinical terminology, they have a theory of mind (ToM) deficit or an impaired capacity of mentalizing (Brüne and Brüne-Cohrs, 2006; Bora et al., 2009). In a study of 38 patients with DSM-IV schizophrenia, Brüne et al. (2007) found a significant correlation between executive planning skills (i.e., neurocognition) and mental state attribution abilities (i.e., social cognition). Considering that executive processes are associated with motor soft signs (see above), the selectivity of the correlation between mental state attribution abilities and executive processes (Abdel-Hamid et al., 2009) is suggestive of a possible link between motor sequencing difficulties and ToM deficits in schizophrenia.

In the present study, based on indirect evidence suggesting a common pathway of NSS, neurocognition, and social cognition in schizophrenia, we tested the hypothesis that NSS in general and motor sequencing difficulties in particular are correlated with ToM deficits in a group of stabilized patients with schizophrenia.

2. Methods

2.1. Participants

Ninety patients (58 men and 32 women) with schizophrenia according to DSM-IV criteria participated in the present study. All patients were recruited from the psychiatric day hospital of the University of Rome Tor Vergata Medical School. All patients were clinically stable and had no history of acute psychotic exacerbation for at least 3 months. Medication doses were calculated in chlorpromazine equivalents (Davis, 1974; Woods, 2003). The diagnosis of schizophrenia was made by at least two experienced clinicians. The exclusion criteria of the study were as follows: (1) any organic brain disorder; (2) any history of severe head trauma; (3) mental handicap/learning disability; and (4) any history of substance dependence/abuse. Before the examination, the patients signed an informed consent. The study was approved by the local ethics committee and carried out in accordance with the Declaration of Helsinki.

2.2. Assessment of neurological soft signs

NSS were assessed using the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989). The NES is a structured scale providing scores in four subscales (sensory integration, motor coordination, sequencing of complex motor acts and “others”). It captures a wide range of neurological signs within 26 items. Each item is rated on a scale from zero to two (zero, relatively normal; one, some disruption; and two, major disruption) according to standardized instructions. The sensory integration subscale includes audio–visual integration, stereognosis, graphesthesia, extinction and right/left confusion. The motor coordination subscale includes tandem walk, rapid alternating movements, finger/thumb opposition and the finger-to-nose test. Sequencing of motor acts includes the fist-ring test, the fist-edge-palm test, the Ozeretski test and rhythm-tapping test B. The “others” subscale comprises adventitious overflow, the Romberg test, tremor, memory, mirror movements, rhythm-tapping test A, synkinesis, convergence, gaze impersistence, glabellar reflex, snout reflex, grasp reflex and suck reflex. The higher the score, the greater the neurological impairment. To measure the severity of the neurological impairment, the total score and scores for each of the four subscales were used. The scores of the items assessed on both the right and left sides of the body were added. The NSS were rated by an experienced neurologist (S.R.) who applied the NES full instructions for training guidelines.

2.3. Theory of mind assessment

Most common measures to assess ToM are false belief understanding tasks (Frith and Corcoran, 1996). In their simplest form, these tasks measure the subject's ability to understand that someone can act on the basis of beliefs that misrepresent reality (first-order false belief). In a more complicated version of these tasks, participants have to infer the false belief of one character about the belief of a second character (second-order false belief). In this study, we used verbal measures of false belief understanding. Participants were requested to understand and answer questions based on verbal stories. All participants were given one first-order and one second-order false belief tests of ToM. The first-order ToM task was the Cigarette task (Pickup and Frith, 2001), a version of the object transfer task in which the subject is told a story in which a character's belief about the location of a target object becomes false when the object is moved without the character's knowledge. The second-order ToM task was the Burglar story (Happé and Frith, 1994), where the participant must attribute a story character's false belief about another character's belief that is investigated by asking a specific question to the participant.

The two stories were read aloud to the subjects. After the story was read out, two questions were asked. The first question could only be answered with knowledge of the mental state of one of the characters (ToM question) and reflected that characters' false belief about the situation. As a measure of comprehension, subjects were asked a second question about the reality of the situation (reality question).This question could be answered correctly without the use of mentalizing abilities. The second question also served as a measure of how well the subject had remembered the story. If the subject gave the wrong answer to the reality question then the answer to the ToM question for that story was ignored in order to ensure that the measure reflected a deficit in mentalizing rather than mnemonic or comprehension ability. ToM assessment and examination of NSS were performed on the same day by different raters who were blind to the results of the other assessment.

2.4. Statistical analysis

Pearson coefficients of correlation (r) were used to calculate bivariate correlations between variables. Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used to compare groups on continuous dependent variables. Homogeneity of variance was tested by Levene's test. Analysis was performed on a personal computer using SPSS for Windows, version 17.0 (SPSS, Inc., Chicago, Ill.).

3. Results

Table 1 reports demographic and clinical data for the entire sample. Handedness of the participants was as follows: right, 85%; left, 4%; mixed, 11%. As expected, the number of participants who passed the second-order false belief task ($N=42$ or 47%) was lower than the number of participants solving the first-order false belief task ($N=64$ or 71%). Table 2 reports zero-order correlations between the NES subscales and demographic and clinical variables. Sensory integration was negatively correlated with level of education. Older age, lower education, and longer illness duration were associated with worse scores on both the motor coordination subscale and the sequencing of complex motor acts subscale. Longer illness duration was positively correlated with the “others” subscale. Antipsychotic drug treatment was not correlated with any of the NES subscales.

To assess the relationship between theory of mind deficits and NSS, we carried out two-way ANOVAs with each of the four subscales of the NES as dependent variables. Grouping variables were gender and the ability to pass false belief tasks. Separate analyses were conducted for first-order (ToM-1) and second-order (ToM-2) false belief tasks. Table 3 reports the results of the ANOVAs tests. Neither gender nor ToM measures were associated with sensory integration, motor coordination and the “others” subscale. By contrast, both false belief tasks were related to sequencing of complex motor acts. Participants who were not able to pass first- or second-order false belief tasks showed greater impairment with regard to sequencing of complex motor acts