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Neuropsychological performance and auditory event related potentials in schizophrenia patients and their siblings: A family study

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ABSTRACT

Background: Various neuropsychological domains, and P300 auditory event-related potentials (ERP) and mismatch negativity (MMN) exhibit abnormalities in schizophrenia patients and their first-degree relatives. The aims of this study were to compare cognitive and P300/MMN measurements in schizophrenia patients, their siblings, and controls, and to identify the degree of familial influence on each measure.
Methods: Thirty patients diagnosed with schizophrenia according to DSM-IV, 20 unaffected siblings and 25 healthy controls were able to complete all neuropsyhological and neurophysiological assessments. All participants were administered SCID-I and the patients were also evaluated regarding symptom severity and functioning. Neuropsychological battery testing results and P300/MMN measurements were obtained for all the participants.
Results: Both schizophrenia patients and their siblings had lower working memory, as measured by the Auditory Consonant Trigram Test (ACT), and lower MMN amplitude scores than the controls. In addition, the patients had lower attention, verbal memory, executive function, visuomotor speed, and figural memory scores than both the siblings and controls, and lower verbal fluency scores than controls. MMN and P300 amplitudes were lower and P300 latency longer in the schizophrenia patients, as compared to controls. P300 latency was also longer in the schizophrenia patients as compared to siblings and, MMN amplitudes were significantly lower in the siblings compared to controls. Working memory performance measured by ACT significantly predicted inclusion in both the patient and sibling groups and showed significant familial influence. MMN amplitude significantly predicted inclusion only to the patient group and did not show significant familial influence.
Conclusion: The schizophrenia patients exhibited impairment in various cognitive domains and P300/MMN measurements, versus impairment only in working memory and MMN amplitude in their siblings. Working memory seems to have a relatively strong familial influence among all the neuropsychological and neurophysiological parameters evaluated.

1. Introduction

Cognitive impairment in schizophrenia patients affects several neuropsychological domains—primarily short and long-term memory, attention, executive functions, and working memory (Saykin et al., 1991; Strous et al., 1995; Javitt et al., 1997). Furthermore, deficits in attention, working memory, and executive functions have also been observed in schizophrenia patients' unaffected relatives and twins (Glahn et al., 2003; Pirkola et al., 2005; Delawalla et al., 2006; Heydebrand, 2006). Research on cognitive functions in schizophrenia-spectrum disorder patients, in first-degree relatives of schizophrenia patients, in individuals with a high risk of psychosis, and in individuals with schizotypal personality features all suggest that cognitive impairment is genetic or familial and may predispose individuals to schizophrenia (Nuechterlein et al., 2002; Mitropoulou et al., 2005; Gooding et al., 2006; Heydebrand, 2006; Keefe et al., 2006; Bove, 2008; Seidman et al., 2010).

Neuropsychological findings in schizophrenia are supported by findings of a deficient neurophysiological correlate of auditory sensory memory—the event-related potential (ERP) component referred to as mismatch negativity (MMN) (Javitt et al., 1995). Mismatch negativity is generated whenever the auditory system detects a deviant sound relative to a background of repetitive standard sound elicited in an

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experimental paradigm referred to as oddball (Winkler et al., 1996), and is recorded while the subject's attention is directed elsewhere while reading, performing a visual task, or watching a video (Michie et al., 2002). The MMN reflects the properties of an automatic, memory-based comparison process. As the MMN occurs even in the absence of conscious and effortful attention, it appears to index a pre-attentive form of sensory (echoic) memory (Turetsky et al., 2007). The reduced MMN amplitude in schizophrenia reflects a deficit in the temporal integration of auditory information during the early stages of auditory processing (Michie, 2001). Furthermore, clinically unaffected family members of schizophrenia patients, children at risk of developing schizophrenia, and recent-onset patients have all been reported to have reduced MMN amplitudes. As such, MMN is considered a promising biological vulnerability marker for schizophrenia (Michie et al., 2002; Price et al., 2006; Turetsky et al., 2007).

Another auditory ERP that exhibits abnormality in schizophrenia is P300, which is observed approximately 300 ms after stimulus onset. P300 is regarded as an index of information processing in the human brain (Donchin and Coles, 1988). Similar to MMN, P300 is elicited using an oddball paradigm in which a deviant stimulus is interspersed among regularly occurring standard stimuli. The P300 event-related brain potential is an index of endogenous cognitive processes that include directed attention, the contextual updating of working memory, and attributing salience to a deviant stimulus (Turetsky et al., 2007). Since Roth and Cannon (1972) first reported ERP abnormalities in schizophrenia patients, including reduced P300 amplitude, numerous follow-up studies have confirmed their findings. Similar to MMN, P300 is also considered a biological vulnerability marker for schizophrenia, as studies of the siblings and offspring of schizophrenia patient probands show that they also have reduced P300 amplitudes (Frangou et al., 1997; Karoumi et al., 2000; Turetsky et al., 2000, 2007).

Although the mode of inheritance in non-Mendelian and complex, it has long been considered that the heritability of schizophrenia is high (Delisi, 1997). There is a lack of schizophrenia studies in which auditory ERP measures are examined in combination with neuropsychological measures in patients and their first-degree relatives. The study was based on the hypothesis that the patients and their siblings would exhibit a continuum regarding neuropsychological and auditory ERP measures, and that the schizophrenia patients would have the lowest neuropsychological performance scores and the most significant P300/MMN abnormalities, followed by their siblings and the controls. It was also assumed that certain neurocognitive and auditory ERP measures would predict inclusion in both the patient and sibling groups showing significant familial influence.

2. Methods and materials

2.1. Study site and participants

This study was conducted at Hacettepe University, Faculty of Medicine, Department of Psychiatry, Ankara, Turkey. The study included 33 consecutive schizophrenia patients (in- and out-patients) diagnosed according to the DSM-IV criteria (American Psychiatric Association (APA), 1994) that were in a clinically stable condition for at least 1 year, agreed to participate, and had siblings within the same age range who agreed to participate. The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used to confirm the diagnosis of schizophrenia and to rule out any other Axis I disorders. The patients' siblings were selected from brothers and sisters that were matched for age, gender, and level of education. Healthy controls were also matched with the patients in terms of age, gender, and level of education. Among the siblings evaluated, 36 agreed to participate and had a negative psychiatric history. In addition, 25 controls deemed healthy based on history and with a negative family history for schizophrenia and other psychotics disorders were also included. From this sample, 30 patients, 20 siblings and 25 controls were able to complete all neuropsychological and neurophysiological assessments and thus only their data will be presented in this work. Thirty patients and 20 siblings came from a total of 30 families. In 12 of these families one subject was rated, in 16 families two subjects were rated, in 2 families three subjects were rated.

Following recruitment SCID-I was administered to rule out any Axis I disorder in the siblings and controls. None of the siblings and controls had a major Axis I psychiatric disorder.

For neuropsychological assessments mental retardation and less than 5 years of formal education were additional exclusion criteria for all the participants. IQ level was not formally tested to maximize the participants' compliance with the study protocol, which included an already large neurocognitive test battery. The inclusion criterion of at least 5 years of formal education was considered a predictor of a normal IQ level (Barber, 2005). Use of the short-acting benzodiazepine alprazolam was permitted for the patients, but not within 24 h of neuropsychological testing and ERP recording.

Manual dexterity was measured using the finger-tapping test and significant differences regarding this parameter were not observed between the groups. All the participants reported that they had normal hearing. The Hacettepe University Faculty of Medicine Research Ethics Committee approved the study protocol. Written informed consent was obtained from all the participants prior to commencement of the study.

2.2. Study assessments

2.2.1. Clinical assessments

The patients were administered the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Kostakoglu et al., 1999), Clinical Global Impression (CGI) Scale (Guy, 1976), and Global Assessment of Functioning (GAF) Scale (American Psychiatric Association (APA), 1994) to assess psychopathology and global functioning. All of the patients' clinical assessments were conducted by the same researcher (A.E.S), who was not blinded to the study groups and had received formal PANSS training prior to the study. Neuropsychological and auditory ERP measures were performed in all the participants on 2 consecutive days.

2.2.2. Neuropsychological assessments

A neuropsychological test battery was administered to all the participants, which consisted of the following tests reported to be valid and reliable for use in Turkey: The Rey Auditory Verbal Learning and Memory Test (RAVLT, verbal memory) (Vakil and Blachstein, 1993; Açıkgöz, 1995), the Digit Span Forward Test (DS-FT, auditory attention), Digit Span Backward Test (DS-BT, working memory) and Figural Memory Test (FMT, figural memory) from the Wechsler Memory Scale-Revised Edition (Wechsler, 1987; Karakaş and Kafadar, 1994), the Controlled Word Association Test and Category Fluency Test (CWAT and CFT, verbal fluency) (Bingöl and Haktanır, 1994; Lezak, 1995; Umaç, 1997), the Wisconsin Card Sorting Test (WCST, executive functions) (Heaton et al., 1993; Karakaş et al., 1996), the Trail Making Test-Part B (TMT-B, visuomotor speed) (Spreen and Strauss, 1998), the Auditory Consonant Trigram Test (ACT, working memory) (Stuss et al., 1987; Anıl et al., 2003), and the Finger-Tapping Test (FTT, motor speed) (Yeudall et al., 1987; Spreen and Strauss, 1998). Time to complete the battery was about 1.5 h per participant.

2.2.3. Auditory ERP recordings

During the ERP recording sessions the participants were seated comfortably in a silent room. Stimuli were presented dichotically using an STIM^2 system (Compumedics Neuroscan, Charlotte, NC). Etymotic ER1 insert earphones were used for sound delivery. A frequency deviance P300 and a duration deviance MMN oddball paradigm were used. In both paradigms, the stimuli were presented in a pseudorandom order such that the number of standard stimuli between consecutive deviants was uniformly distributed between 3 and 7; the probability of