Journal of Psychiatric Research 47 (2013) 1623–1629

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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

Schizophrenia-like neurophysiological abnormalities in 22q11.2 deletion syndrome and their association to *COMT* and *PRODH* genotypes

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ARTICLE INFO

Article history:
Received 14 March 2013
Received in revised form
22 June 2013
Accepted 5 July 2013

Keywords:
22q11.2DS
Catechol O-methyltransferase
Proline dehydrogenase
Endophenotype
Sensory gating
Mismatch negativity

ABSTRACT

22q11.2 deletion syndrome (22q11.2DS) is a common genetic risk factor for the development of schizophrenia. We investigated two neurophysiological endophenotypes of schizophrenia – P50 sensory gating and mismatch negativity in 22q11.2DS subject and evaluated their association with catechol O-methyltransferase (*COMT*) and proline dehydrogenase (*PRODH*) genetic variants. We also assessed the association of neurophysiological measures with schizophrenia-like symptomatology in 22q11.2DS. Fifty-nine subjects, 41 with 22q11.2DS and 18 typically developing controls, participated in the study. The participants with 22q11.2DS were genotyped for the *COMT Val*^{158}*Met* (rs4680) and *PRODH Gln*^{19}*Pro* (rs2008720) and *Arg*^{185}*Trp* (rs4819756) polymorphisms. Following psychiatric evaluation, all the participants underwent neurophysiological recordings and executive function assessment. The 22q11.2DS group showed poorer sensory gating of the P50 response than the controls. Within the 22q11.2DS group, the *COMT Met* allele was associated with poorer sensory gating, while both the *COMT Met* allele and the *PRODH Pro-Arg* haplotype were associated with smaller mismatch negativity amplitudes. Smaller mismatch negativity amplitudes predicted greater impairment of executive functions and greater severity of schizophrenia-like negative symptoms in 22q11.2DS. The current study demonstrates that sensory gating impairments that are typical of schizophrenia are found in 22q11.2DS subjects. Our results further suggest that *COMT* and *PRODH* genetic variations contribute to sensory gating and mismatch negativity schizophrenia-like impairments in 22q11.2DS, possibly via dopaminergic/glutamatergic networks. The associations of mismatch negativity impairments with increased severity of schizophrenia-like negative symptoms and poorer executive functions performance in our 22q11.2DS sample suggest that mismatch negativity is a potential endophenotype for schizophrenia in 22q11.2DS.

1. Introduction

The 22q11.2 deletion syndrome (22q11.2DS) is the most common of all microdeletion syndromes and one associated with high rates of psychiatric morbidity, such as schizophrenia, which occurs in up to one-third of the affected individuals (Gothelf et al., 2008). Two of the approximately 30 genes within the minimal deleted region that are suspected to affect susceptibility for schizophrenia are catechol-O-methyltransferase (*COMT*) and proline dehydrogenase (*PRODH*) (Gothelf et al., 2008; Vorstman et al., 2008; Willis et al., 2008). The *COMT* gene encodes for the COMT enzyme, which is responsible for dopamine degradation and plays an especially important role in the prefrontal cortex (PFC) (Chen et al., 2004). The *PRODH* encodes for the

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http://dx.doi.org/10.1016/j.jpsychires.2013.07.004

PRODH enzyme, a mitochondrial proline dehydrogenase that catalyzes the first step in proline catabolism. *PRODH* hemizygous deletion is thought to alter the glutamatergic and dopaminergic transmission (Henzi et al., 1992; Paterlini et al., 2005). To further investigate the role of *COMT* and *PRODH* in the 22q11.2DS susceptibility for schizophrenia, we measured two neurophysiological endophenotypes of schizophrenia, mismatch negativity (MMN) and P50 sensory gating (P50-SG) (Michie, 2001; Adler et al., 1998).

The MMN is an involuntary change-specific component of the auditory event-related potential (ERP) elicited by any discriminable change in repetitive stimulation (Näätänen et al., 1978). P50-SG is a measure of the suppression of the second P50 relative to the first P50 ERP in a paired-click paradigm presumed to reflect the individual's ability to filter out repetitive, irrelevant stimuli and thus minimize information overload (Freedman et al., 1996). While the MMN is mediated by the N-methyl-D-aspartate (NMDA) receptor (Javitt et al., 1996) and P50-SG is mediated mainly by nicotinic receptors (Adler et al., 1998), dopaminergic modulatory effects have also been implied both for MMN and P50-SG (Adler et al., 1986; Baker et al., 2005; Mann et al., 2007).

To date, there are only few reports on the genotype–neurophysiological phenotype associations in 22q11.2DS (Baker et al., 2005; De Koning et al., 2012; Sobin et al., 2005; Vorstman et al., 2008). Neurophysiological abnormalities were found in MMN, prepulse inhibition (PPI) and smooth pursuit eye movement (SPEM) of subjects with 22q11.2DS (Baker et al., 2005; De Koning et al., 2012; Sobin et al., 2005; Vorstman et al., 2008). Individuals with 22q11.2DS *COMT Met* carriers were found to have aberrant PPI and MMN amplitudes, but no *COMT* effect was detected for P50-SG (Baker et al., 2005; De Koning et al., 2012; Vorstman et al., 2008). To our knowledge, there have been no previous reports on the effect of *PRODH* genotypes on the neurophysiological endophenotypes in 22q11.2DS.

The main objective of the current study was to comprehensively investigate neurophysiological endophenotypes of schizophrenia in 22q11.2DS and to assess their associations with *COMT* and *PRODH* polymorphisms in the remaining intact chromosome 22. Another goal was to evaluate the association between the detected neurophysiological abnormalities in 22q11.2DS and the degree of schizophrenia-like symptoms and executive function (EF) deficit. Our study hypotheses were: (1) Subjects with 22q11.2DS would show neurophysiological deficits typical to schizophrenia, i.e., smaller MMN amplitudes and poorer P50-SG compared to typically developing (TD) controls; (2) *COMT* and *PRODH* variants in 22q11.2DS subjects would modulate MMN amplitudes and P50-SG; (3) the neurophysiological deficits in 22q11.2DS subjects would be positively associated with the degree of EF impairments and the severity of schizophrenia-like symptoms.

2. Methods

More detailed information can be found in Supplementary methods.

The study protocol was approved by the Institutional Review Board. After complete description of the nature of this study to the subjects and their parents or guardians, we obtained written informed consent from all participants and from the parents of minors.

2.1. Participants

The study groups consisted of 41 subjects with 22q11.2DS and 18 TD controls. The individuals with 22q11.2DS were recruited from the Behavioral Neurogenetics Center at a large tertiary referral center in Israel. The controls were recruited through advertisements within the local community and major psychopathology among them was ruled out before study entry. Six (14.63%) of the 22q11.2DS subjects had a psychotic disorder, of whom three met the DSM-IV-TR criteria for schizophrenia, and one each for a schizoaffective disorder, a brief psychotic disorder and a psychotic depressive disorder.

2.2. Genotyping

Diagnosis of all subjects with 22q11.2DS was confirmed by fluorescence in situ hybridization (FISH) testing and multiplex ligation-dependent probe amplification (MLPA) (Michaelovsky et al., 2012; Vorstman et al., 2006). All subjects had deletions of both the *COMT* and *PRODH* genes. Genotyping assays of *COMT* $Val^{158}Met$ polymorphism (rs4680) as well as *PRODH* $Gln^{19}Pro$ (rs2008720) and $Arg^{185}Trp$ (rs4819756) polymorphisms are described in the Supplementary methods. We chose the *COMT* $Val^{158}Met$ polymorphism as several studies have indicated that this genetic variant is associated with psychiatric morbidity and brain dysfunction in 22q11.2DS and is affecting the enzymatic activity of COMT (Gothelf et al., 2005; Baker et al.,2005; de Koning et al., 2012; Chen et al., 2004). The *PRODH* variants were chosen because they have been reported to alter *PRODH* enzymatic activity (Bender et al., 2005; Raux et al., 2007) and their allelic distribution showed two common variants, and hence enabled testing for associations.

2.3. Neurophysiology

A comprehensive review on the recording parameters, neurophysiological paradigms and waveform analysis can be found in the Supplementary methods.

All the participants first underwent the MMN paradigm which was followed by the P50-SG paradigm, separated by a 5-min break. None of them had smoked for at least 2 h before undergoing electroencephalographic (EEG) testing. Prior to undergoing the neurophysiological evaluation, the subjects completed audiometric testing to determine their hearing thresholds, ensuring that they were $\leq$35 dBHL in the frequencies 250–8000 Hz (Zarchi et al., 2011). Neurophysiological recordings took place in an electroacoustic shielded room using five scalp electrodes and an electrooculogram. The MMN paradigm was constructed according to Näätänen et al.'s "optimal paradigm" (Näätänen et al., 2004), allowing the recording of MMNs for several auditory deviants in a single session, i.e., frequency, intensity, directionality, duration and a silent gap deviants. The sensory gating paradigm was constructed according to Nagamoto et al.'s paired-click paradigm (Nagamoto et al., 1989). Gating was scored as the ratio of the amplitude of the P50 response to the second click (S2) divided by the amplitude of the P50 response to the first click (S1).

2.4. Psychiatric and EF assessments

The 22q11.2DS subjects and their parents were interviewed by experienced clinicians (DG and TG) using the Hebrew version of the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime (K-SADS-PL) (Kaufman et al., 1997). Adult participants and their parents (when available) were interviewed with the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID) (First et al., 1996). All 22q11.2DS subjects were administered the Positive and Negative Syndrome Scale (PANSS) to evaluate the existence and severity of schizophrenia symptoms (Kay et al., 1987). EF were evaluated using the Simon task – taxing working memory, inhibition and mental flexibility (see Supplementary methods) (Davidson et al., 2006).