Dopamine in high-risk populations: A comparison of subjects with 22q11.2 deletion syndrome and subjects at ultra high-risk for psychosis

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ARTICLE INFO
Keywords:
22q11 deletion syndrome
Ultra High Risk Psychosis
Dopamine
SPECT

ABSTRACT
Striatal dopamine (DA) dysfunction has been consistently reported in psychotic disorders. Differences and similarities in the pathogenesis between populations at clinical and genetic risk for developing psychosis are yet to be established. Here we explored markers of dopamine (DA) function in subjects meeting clinically ultra-high risk criteria for psychosis (UHR) and in subjects with 22q11.2 deletion syndrome (22q11DS), a genetic condition associated with significant risk for developing psychotic disorders.

Single Photon Emission Computed Tomography (SPECT) with 123I-labelled iodobenzamide ([123I]IBZM) was used to measure striatal DA D2,3 receptor binding potential (D2RB PND). Also, peripheral DAergic markers were assessed in serum and urine (plasma prolactin (pPRL), plasma homovanillic acid (pHVA) and urine DA (uDA)).

No significant difference in striatal D2RB PND was found between UHR and 22q11DS subjects. Compared to UHR subjects, pPRL and pHVA were lower and uDA levels were higher in the 22q11DS subjects. However, after correcting for age and gender, only pPRL was significantly lower in the 22q11DS patients.

These results may suggest that there are differences in DAergic markers between subjects with UHR and with 22q11DS that may reflect differences in the pathways to psychosis. However, bigger samples are needed to replicate these findings.

1. Introduction
Psychotic disorders, of which schizophrenia is the most severe form, are characterized by delusions, hallucinations, and formal thought disorder. Vulnerability to psychotic disorders, is dependent on a complex interaction of genetic and environmental factors (van Os et al., 2010), and the pathogenesis is hypothesized to involve altered neurodevelopmental, neurofunctional and neurochemical mechanisms (Bassett et al., 2001; Boot and van Amelsvoort, 2012; Fusar-Poli et al., 2012; Stone et al., 2007). Striatal dopaminergic (DAergic) dysfunction is hypothesized to be the final common pathway in psychosis (Abi-Dargham et al., 2009; Howes et al., 2012; Howes and Kapur, 2014, 2009; Howes and Murray, 2014; Kegeles et al., 2010).

22q11.2 deletion syndrome (22q11DS) is one of the most common recurrent copy number variant disorders caused by a microdeletion on the long arm of chromosome 22 (Jonas et al., 2014). Subjects with this syndrome have a 30-fold risk of developing schizophrenia spectrum disorders (Bassett et al., 2003; Murphy, 2001, 1999; Schneider et al., 2014), and the deletion is among the highest genetic risk factors for the development of psychosis (Murphy, 1999). In 22q11DS, it has been hypothesized that the increased risk for developing psychosis may be at least partially due to altered dopamine (DA) functioning resulting from reduced dosage and expression of the catechol-O-methyltransferase (COMT) gene, which is located in the deleted 22q11.2 region (Graf et al., 2001; Gothelf et al., 2005; Fallgatter and Lesch, 2007; Boot et al., 2008; Gothelf et al., 2014) and which supposedly leads to increased DA levels. The COMT enzyme is important for degrading DA. Indeed, Gothelf et al. (2014) found a reduction of approximately 50% in COMT mRNA, protein and enzyme activity levels in peripheral cells of patients with 22q11DS.

Our group previously showed disrupted peripheral DA metabolism in adults with 22q11DS patients compared to age- and gender matched healthy controls (Boot et al., 2008), although Evers et al. (2014) did not find altered peripheral DA levels in 22q11DS patients compared to healthy controls in a larger sample with a broader...
phenotype including patients on antipsychotic medication. However, our group did not find differences in striatal synaptic D_{2/3} receptor binding (assessed with [^{123}I]iodobenzamide and single photon emission computed tomography ([^{123}I]-IBZM SPECT)) between 22q11DS and healthy controls in the same subjects (Boot et al., 2010). Lower D_{2R} BP_{ND} may represent higher DA levels as DA may compete with the radiotracer [^{123}I]IBZM to bind to DA D_{2/3} receptors (competition model; Laruelle, 2000).

A different group at increased risk of psychosis are patients that meet the Ultra High-Risk (UHR) criteria for developing psychosis. These criteria as established by Yung et al. (2004) include subthreshold psychotic symptoms and approximately 30% of patients meeting UHR criteria develop psychosis within 2 years. Excessive pre-synaptic striatal DAergic activity, assessed with [^{18}F]DOPA and positron emission tomography (PET), has been found in UHR subjects who developed psychosis in comparison with healthy controls (Howes et al., 2011). The same research group recently replicated these findings in an independent sample (Egerton et al., 2013). These results suggest that pre-synaptic elevated DA synthesis predate the onset of psychosis. Bloemen et al. (2013) did not find significant differences in changes in baseline striatal DA D_{2/3} receptor binding between UHR subjects and healthy controls. However, in that same study, synaptic DA concentration, assessed with a DA depletion paradigm with alpha-methyl-para-tyrosine (AMPT), significantly correlated with symptom severity (Bloemen et al., 2013). Moreover, DA depletion decreased positive symptoms, suggesting that increased synaptic DA concentrations are a state characteristic for psychosis.

At present it is unclear whether these two profiles with a high risk of developing psychosis represent similar or different underlying dopaminergic pathways to psychosis. We previously reported differences in peripheral markers between 22q11DS patients and healthy controls (Boot et al., 2010), but in a separate report by our group, no such difference was found for UHR subjects compared to controls (Bloemen et al., 2013). However, it is unknown how these two high-risk groups relate to each other in terms of DAergic markers. Therefore, directly comparing DAergic markers between these unique groups may provide important insight on the pathways leading to psychosis in different high-risk populations. In this study we explored for the first time whether there are differences in DAergic markers between genetic and clinical risk profiles for psychosis by comparing baseline striatal D_{2/3} receptor binding and peripheral DAergic markers between 22q11DS subjects and UHR subjects.

2. Methods

This study was approved by the medical ethics committee of the Academic Medical Center of the University of Amsterdam, the Netherlands. All participants signed informed consent prior to participation after the procedure had been fully explained to them.

2.1. Subjects

Participants were 22 non-psychotic adults with 22q11DS (8 males and 14 females) aged 18–43 years, 16 UHR subjects (12 males and 4 females) aged 18–29 years and 38 healthy controls (27 males and 11 females) aged 18–48 years. All 22q11DS and UHR subjects were antipsychotic and psychostimulant-naïve at the time of the study. The subject characteristics are described in Boot et al. (2008, 2010, and Bloemen et al. 2013). The healthy control samples described in these studies were recruited independently and did not overlap. 22q11DS subjects were recruited via the Dutch 22q11DS family association and through the departments of four Dutch Clinical Genetics Centers. UHR subjects were recruited through the early psychosis department of the Academic Medical Center. Healthy control subjects were recruited through local advertisement. Although UHR criteria include subjects with a first-degree relative with a psychotic disorder who experienced a decline in functioning (Yung and McGorry, 2007), none of the recruited subjects in our sample had a first-degree relative with a psychotic disorder. Therefore, genetic components in the UHR group are considered minimal. Consequently, all UHR subjects were recruited on basis of having attenuated psychotic symptoms. Exclusion criteria for all study subjects were a current diagnosis or history of psychiatric disorders, present use or lifetime history of substance dependence or abuse, comorbid or past severe medical conditions, participation in research with radioactive load one year prior to participation, and pregnancy determined with a urine β-human chorionic gonadotrophin (β-HCG) test. For all 22q11DS subjects, the deletion was confirmed by fluorescent in-situ hybridization (FISH). All imaging subjects were instructed to refrain from alcohol, nicotine and caffeine 24 h prior to scanning.

2.2. Clinical measures

UHR was established with the “comprehensive assessment of at risk mental state” (CAARMS) (Yung et al., 2004) by a psychiatrist or experienced research psychologist. Psychotic symptom severity was assessed for all subjects using the positive and negative syndrome scale (PANSS) (Kay et al., 1987). The PANSS consists of 3 subscales: positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items) with scores ranging from 1 (absent) to 7 (extreme). To estimate a full scale intelligence quotient (FSIQ), a shortened version of the Wechsler Adult Intelligence Scale III was conducted.

2.3. D_{2R} BP_{ND} and peripheral dopaminergic markers

To measure striatal D_{2/3} receptor binding potential (D_{2R} BP_{ND}), subjects underwent [^{123}I]IBZM (specific activity > 200 MBq/nmol and radiochemical purity > 95%) imaging using the validated equilibrium/constant infusion technique. The study was performed on a high-resolution brain-dedicated SPECT system (Neurofocus). Axial slices were acquired in 5 mm steps and each imaging session consisted of 12 – 13 slices with 5 min scanning time per slice. Briefly, all images were corrected for attenuation and reconstructed in a three-dimensional mode (Booij et al., 1997). Region of interest (ROI) analyses were performed using fixed ROI templates for the left and right striatum (representing specific binding) and occipital cortex (representing non-specific binding) and placed on four consecutive axial slices with the highest striatal binding. To account for interpersonal variation, the fixed ROIs were moved for optimal fitting without changing size and shape. The mean of all slices was calculated for all ROIs and subsequently the D_{2R} BP_{ND} was calculated as the ratio of specific (striatum) to non-specific activity (occipital lobe) (total activity in striatum minus activity in occipital cortex, divided by activity in occipital cortex). For more details about the SPECT acquisition protocol, image reconstructions, the reader is referred to our previous reports (the UHR population described by Bloemen et al. (2013) and the 22q11DS population by Boot et al. (2010)). All SPECT data were analyzed blind to clinical data, by the same investigator (E.B.). In addition, blood samples were drawn to determine plasma prolactin (pPRL) and homovanillic acid (pHVA). Urine samples were collected for determination of DA (uDA). For details regarding analyses of peripheral DAergic markers please refer to our previous studies (Boot et al., 2008, 2010; Bloemen et al., 2013).

2.4. Statistical analysis

All data was analyzed using IBM SPSS Statistics 20 with a 2-sided alpha of 0.05. Between-group differences for gender distribution were tested using a χ^2 test. Between-group (UHR, 22q11DS and healthy controls) differences in clinical measures were analyzed using one-way analyses of variance (ANOVA). First, to assess whether potential differences in striatal D_{2R} BP_{ND} and peripheral DAergic markers deviate from healthy subjects we performed an additional one-way ANOVA with the three groups (UHR, 22q11DS and healthy controls) for these
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