Lower $[^{18}F]$fallypride binding to dopamine D$_{2/3}$ receptors in frontal brain areas in adults with 22q11.2 deletion syndrome: a positron emission tomography study

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Abstract

**Background.** The 22q11.2 deletion syndrome (22q11DS) is caused by a deletion on chromosome 22 locus q11.2. This copy number variant results in haplo-insufficiency of the catechol-O-methyltransferase (COMT) gene, and is associated with a significant increase in the risk for developing cognitive impairments and psychosis. The COMT gene encodes an enzyme that primarily modulates clearance of dopamine (DA) from the synaptic cleft, especially in the prefrontal cortical areas. Consequently, extracellular DA levels may be increased in prefrontal brain areas in 22q11DS, which may underlie the well-documented susceptibility for cognitive impairments and psychosis in affected individuals. This study aims to examine DA D$_{2/3}$ receptor binding in frontal brain regions in adults with 22q11DS, as a proxy of frontal DA levels.

**Methods.** The study was performed in 14 non-psychotic, relatively high functioning adults with 22q11DS and 16 age- and gender-matched healthy controls (HCs), who underwent DA D$_{2/3}$ receptor $[^{18}F]$fallypride PET imaging. Frontal binding potential (BP$_{ND}$) was used as the main outcome measure.

**Results.** BP$_{ND}$ was significantly lower in adults with 22q11DS compared with HCs in the prefrontal cortex and the anterior cingulate gyrus. After Bonferroni correction significance remained for the anterior cingulate gyrus. There were no between-group differences in BP$_{ND}$ in the orbitofrontal cortex and anterior cingulate cortex.

**Conclusions.** This study is the first to demonstrate lower frontal D$_{2/3}$ receptor binding in adults with 22q11DS. It suggests that a 22q11.2 deletion affects frontal dopaminergic neurotransmission.

Introduction

The 22q11.2 deletion syndrome (22q11DS) is a relatively common genetic disorder, with an estimated prevalence of one in 4000–4000 births. It is characterized by a deletion on locus 22q11.2, a copy number variant that contributes significantly to the risk for psychotic disorders (Murphy et al., 1999; Schneider et al., 2014). 22q11DS has a heterogeneous phenotype including cardiac anomalies (Guo et al., 2017) and several psychiatric problems (Schneider et al., 2014). Cognitive impairments (Oksarsdottir et al., 2004; Bassett et al., 2005; Biswas and Furniss, 2016; Norkett et al., 2017) are part of the core symptoms of the syndrome. Additionally, approximately one in four individuals with 22q11DS develop a psychotic disorder, making 22q11DS one of the greatest known risk factors for developing psychosis (Bassett, 2011). Therefore, it is suggested that 22q11DS represents a valuable model for the study of neurobiological factors underlying both cognitive impairments (Oksarsdottir et al., 2004; Bassett et al., 2005; Biswas and Furniss, 2016; Norkett et al., 2017) and psychotic disorders (Gur et al., 2017). Although the biological factors underlying psychotic disorders and their cognitive symptoms are still poorly understood, there is evidence suggesting for aberrant dopamine (DA) levels in several brain regions (Howes et al., 2012; Fusar-Poli and Meyer-Lindenberg, 2013), including the prefrontal cortex (PFC) (Slifstein et al., 2015).
Alterations in DA neurotransmission are also suggested to underlie some of the psychiatric problems typically seen in 22q11DS (Boot et al., 2008, 2011; Evers et al., 2014; de Koning et al., 2015). These alterations are possibly due to haploinsufficiency (reduced dosage of the gene due to hemizygosity) of the catechol-O-methyltransferase (COMT) gene, located on the deleted region and coding for the enzyme that catalyzes extracellular DA (Chen et al., 2004). Especially frontal DA is thought to be affected by COMT haploinsufficiency (Yavich et al., 2007) in 22q11DS. This could be explained by the relatively low density of the DA transporter in the PFC (Sesack et al., 1998), resulting in a DA dependency of COMT enzyme activity for clearance (Tunbridge et al., 2007). It has been indicated that 50% of the prefrontal DA clearance results from COMT activity (Yavich et al., 2007). Since patients with 22q11DS have only one copy of the COMT gene, which is associated with reduced COMT gene expression (van Beveren et al., 2012) and enzyme concentrations (Gothelf et al., 2014), they may consequently be chronically exposed to abnormally high DA levels (Boot et al., 2008), particularly in the PFC. We previously showed that the COMT functional polymorphism Val158Met indeed affects DA function in 22q11DS (Boot et al., 2011b). 22q11DS Val-hemizygotes have higher post-synaptic striatal DA D_{2/3} non-displaceable receptor binding potential (D_{2/3}R BP_{ND}) compared to carriers with the relatively unstable and less active COMT Met-allele (Boot et al., 2011b), further implicating altered DA neurotransmission.

The COMT Val/Met genotype has also been related to (dys)function of frontal brain regions in the psychosis continuum (Egan et al., 2001; Hernaus et al., 2013). Abnormalities in frontal brain DA have been hypothesized to especially underlie cognitive and negative symptoms of psychotic disorders (Howes and Kapur, 2009; Howes et al., 2012), which may also be true for 22q11DS (Stoddard et al., 2010; Schneider et al., 2014; Tang et al., 2014). Frontal DA neurotransmission has also been related to (impairments in) different neuropsychological functional domains, including memory, motivation, attention, and concentration (Howes and Kapur, 2009; Jonas et al., 2014; Slifstein et al., 2015). In addition, the COMT genotype is found to modulate cognitive functioning, relying on frontal DA neurotransmission, in psychotic disorder (Jonas et al., 2014; Slifstein et al., 2015) and in 22q11DS (Gothelf et al., 2005; de Koning et al., 2012; Carmel et al., 2014). Moreover, the COMT genotype has been implicated in dopaminergic drug effects on cognitive functioning (Schacht, 2016).

In summary, there is evidence for abnormal frontal DA functioning in cognitive impairments, psychotic disorders, and implications for altered DA function in 22q11DS. More insight into the neurobiological factors associated with both psychotic disorder and cognitive deficits in 22q11DS can be gained, by investigating frontal DA function in 22q11DS using in vivo molecular imaging methods.

Neuroimaging techniques consistently showed both aberrant frontal brain anatomy and function as well as an effect of COMT Val/Met genotype in 22q11DS (van Amelsvoort et al., 2001, 2008; Gothelf et al., 2005; Zinkstok and van Amelsvoort, 2005; Kates et al., 2006; Howes et al., 2012; Shashi et al., 2012; van Beveren et al., 2012; Jonas et al., 2014).

In addition, molecular imaging techniques, including [^{11}C] DTBZ- and [^{18}F]fallypride positron emission tomography (PET) and [^{11}C]HFBZM single photon emission computed tomography (SPECT), have been used successfully in 22q11DS to investigate abnormalities in the striatal DA system (Boot et al., 2010; Butcher et al., 2017; van Duin et al., 2018). However, no studies to date have investigated frontal DA signaling in patients with 22q11DS. This can be measured in vivo with PET, using high-affinity radioligands such as the highly selective DA D_{2/3} receptor (D_{2/3}R) radioligand [^{18}F]fallypride, successfully used to probe frontal DA functioning (Lataster et al., 2011; Ceccarini et al., 2012; Hernaus et al., 2013; Nagano Saito et al., 2013).

The present study aimed to investigate, for the first time, frontal D_{2/3}R BP_{ND} in 22q11DS using [^{18}F]fallypride PET. Because of COMT haploinsufficiency in 22q11DS and previously described findings of SPECT and PET studies (Boot et al., 2010, 2011b; Butcher et al., 2017; van Duin et al., 2018), we expected reduced D_{2/3}R BP_{ND} in frontal brain regions compared to healthy controls (HCs), as a proxy marker of chronically increased extracellular frontal DA levels.

**Materials and methods**

**Participants**

Fourteen non-psychotic adult individuals (eight females and six males, mean age = 34.6 years, S.D. = 9.7 years) with 22q11DS and no family history of psychotic disorder were included. They were compared to a previously published (Kasanova et al., 2017, 2018) sample of 18 HCs (12 females and six males, mean age = 38.1 years, S.D. = 15.6 years). Recruitment and exclusion criteria of HC have been described previously (Kasanova et al., 2017, 2018).

All participants were capable of giving written informed consent and did so after receiving full information on the study. Participants were treated in accordance with the Declaration of Helsinki. The study was approved by the Medical Ethical Committee of Maastricht University (The Netherlands) and the RWTH Aachen University ethics committee of Universitäts Klinikum (Germany). The PET protocol was additionally approved by the national authority for radiation protection in humans in Germany (Bundesamt für Strahlenschutz, BFS). Participants received coupons with a total value of €100 for participating in the PET study.

Exclusion criteria for 22q11DS participants were: (1) lifetime history of psychosis as determined by the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998) and/or current or previous use of antipsychotic or stimulant medication, (2) contraindications for MRI and/or PET imaging, (3) pregnancy (verified on the day of the scan using a pregnancy test), (4) current drug use (verified on the day of the scan using a urine drug test).

Two HC participants were cigarette smokers. Given the well-known association between smoking (status) and DA function (Mansvelder and McGehee, 2000), they were asked to refrain from nicotine use on the day of the imaging session. One HC was excluded due to positioning difficulties during scanning. Another HC participant was excluded based on non-compliance with the study procedures. Two 22q11DS participants used the selective serotonin reuptake inhibitors escitalopram (10 mg) or paroxetine (20 mg). Since this may influence DA functioning (Tanda et al., 1994; Damsa et al., 2004) they were asked to refrain from taking their medication on the day of the imaging session. Other participants did not take any psychotropic medication. The final sample consisted of 16 HC and 14 22q11DS participants (Table 1).
Behavioral and physiological assessments

Full scale intelligence quotient (IQ) of the 22q11DS participants was determined using a shortened Dutch version of the Wechsler Adult Intelligence Scale – III (WAIS-III) (Wechsler, 1997) and was assessed on the day of scanning or in a separate session before or after the PET session (mean = 52.8 days, S.D. = 49.8 days). The shortened WAIS-III consists of four subtests: arithmetic and information (verbal IQ) digit-symbol-coding and block patterns (performance IQ) (Wechsler, 1997; Brooks and Weaver, 2005). In the HC group, total IQ was estimated using the Dutch Adult Reading Test (DART) (Schmand et al., 1991).

Other assessments of the HC group were described previously (Kasanova et al., 2017, 2018).

To assess the presence and severity of psychotic symptoms, the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) for psychotic disorders was used.

Image data collection

The [18F]fallypride PET data collection acquired for this research was part of a comprehensive PET acquisition protocol, previously carried out to investigate reinforcement learning task-induced striatal DA release (Kasanova et al., 2017, 2018; van Duin et al., 2018). For the current PET analyses, only the [18F]fallypride sensorimotor control and baseline conditions were considered, including the first 120 min of the scan protocol (Fig. 1). All details of the whole PET procedure and the structural MRI and PET data acquisition have been described previously (Kasanova et al., 2017; van Duin et al., 2018) and additional analyses including the control only condition (excluding the 25 min baseline scan) to confirm reliability of the used method can be found in the Supplementary Materials.

Image processing – dopamine D2/3 receptor binding potential maps – and analysis

Image pre-processing procedures were performed as described previously (Kasanova et al., 2017, 2018; van Duin et al., 2018) using an automatic pipeline in the PMOD brain PNEURO tool (v. 3.8, PMOD Technologies, Zurich, Switzerland) (see Supplementary Materials). For each subject, individual voxel-wise parametric maps of DA D2/3RB PND (Innis et al., 2007) were generated in patient space using the Ichise’s Multilinear Reference Tissue Model 2 (MRTM2) (Ichise et al., 2003). The cerebellum, including the cerebellar hemispheres without the vermis, was used as the reference region, because of its relative lack of D2/3R (Hall et al., 1994). The details of the MRTM2 analyses can be found in the Supplementary Materials. For the regional-based group comparison analysis (HC v. 22q11DS), a predefined prefrontal mask was generated in patient space for each subject according to the Hammers N30R83 atlas (Hammers et al., 2003). This predefined mask included composite and bilateral region of interests (ROIs), for: (1) PFC, including orbitofrontal cortex (OFC), inferior, middle, and superior frontal gyrus, (2) OFC only, including the anterior, medial, lateral, and parietal orbital gyrus, (3) anterior cingulate cortex (ACC), including only the subgenual and presupplemental ACC, and (4) anterior cingulate gyrus (Fig. 2 and online Supplementary Fig. S1).

| Table 1. Demographics and binding potential (BPND) per region of interest (ROI)† |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Between groups | 22q11DS (n = 14) | HC (n = 16) | Test-stat. | p value |
| Demographics | | | | |
| Age | 34.57 | 9.73 | 38.06 | 15.61 | −0.74* | 0.48 |
| IQ | 79.14 | 12.47 | 103.75 | 8.14 | −6.486* | <0.01** |
| Male | female (n) | 6|8 | 4|12 | 1.07 | 0.30 |
| Smoking (n) | 0 | 2 |
| Medication free (n) | 12c | 16 |
| PANSS total score | 33.21 | 3.42 | 7.14 | 0.53 |
| PANSS positive symptoms | 8.14 | 1.66 |
| PANSS negative symptoms | 17.93 | 2.06 |
| BPND [18F]fallypride | | | | | | |
| ROIs | | | | | | |
| PFC | 0.34 | 0.11 | 0.43 | 0.11 | 4.91 | 0.035 |
| OFC | 0.65 | 0.26 | 0.77 | 0.27 | 1.47 | 0.236 |
| ACC | 1.08 | 0.43 | 1.18 | 0.41 | 0.40 | 0.530 |
| Ant cingulate gyrus | 0.35 | 0.10 | 0.49 | 0.11 | 12.07 | 0.002** |

HC, healthy controls; IQ, intelligence quotient; PANSS, positive and negative symptom scale: total score range min 30–max 210, positive and negative symptom score range min 7–max 49, general psychopathology score range min 16–max 112; PFC, prefrontal cortex; OFC, orbito frontal cortex; ACC, anterior cingulate cortex.

* p < 0.01 and survived Bonferroni correction for multiple testing a = t test, b = χ² test, c = 2 participants with 22q11DS used selective serotonin reuptake inhibitors (SSRIs) escitalopram (10 mg) and paroxetine (20 mg).
PET control: Sensori-motor control condition: Participants conducted a sensori-motor control condition prior to the baseline and experimental condition (previously described in Kasanova et al., 2017, 2018). This condition was designed to contain all features of the task of the experimental condition, without the main manipulation of the experimental condition; outcome-based associative learning. This control condition was presented on a 30-inch screen placed in the field of view of the participant. Similar to the experimental condition, images of a stimulus (photographs of actors) appeared on the screen and participants had to choose between one of two items depicted under the stimulus, for instance, indicate whether the actor was male or female, had short or long hair. The participant was instructed before the task that there was no right or wrong answer. No feedback was provided during the task. The control condition consisted of six blocks of 120 trials, in which 18 actors were presented 40 times, lasting approximately 10 min per block with intertrial intervals where the previous stimulus and items were still visible on the screen for 4 s. The sensori-motor control scan lasted 80 min and consisted of a total of 36 frames (6 × 60 s frames + 30 × 120 s frames).

PET baseline condition: During the baseline condition the participants were instructed to lay down and rest in the scanner. The baseline scan lasted 25 min and consisted of 18 (120 s) frames.
Statistical analyses

Statistical analyses were conducted in SPSS (IBM SPSS Statistics version 25.0). Between-group differences in demographic characteristics were investigated using $\chi^2$ and independent sample t tests. Average BPND values within each ROI (PFC, OFC, ACC, anterior cingulate gyrus) were determined and compared between the 22q11DS and HC group using analysis of variance. Post-hoc analyses were conducted to investigate group differences between HC and 22q11DS in BPND in all sub-regions of the frontal ROIs performing an analysis of variance. In the 22q11DS group, to investigate the relation between frontal BPND, IQ, and PANSS scores, Pearson correlation coefficients were calculated with two-tailed tests of significance. The analyses were corrected for $n = 4$ ROIs, using a Bonferroni correction (critical $p$ value $p = 0.05/4 = 0.013$).

Results

Demographic data

Sociodemographic variables of the sample are summarized in Table 1. There were no significant differences between the 22q11DS and the HC group in age ($t = 0.74$, $p = 0.48$) and gender distribution (22q11DS M/F ratio 6/8; HC M/F ratio 4/12; $\chi^2 = 1.07$, $p = 0.30$). As expected, IQ-scores were significantly lower in the non-psychotic [PANSS (Leucht et al., 2005) scores <58] 22q11DS group compared with the HC group ($t = 6.48$, $p < 0.001$), given that impaired cognitive functioning is a core characteristic of the syndrome (Jonas et al., 2014; Schneider et al., 2014; Weinberger et al., 2016).

Frontal $D_{2/3}$R BPND in 22q11DS vs. HC

Compared with HC, adults with 22q11DS revealed a significant lower $D_{2/3}$R BPND in the PFC ($F = 4.91$, $p = 0.035$) and anterior cingulate gyrus ($F = 12.07$, $p = 0.002$) (see Table 1 and Fig. 3, individual data points are plotted in online Supplementary Fig. S2), suggesting lower receptor BPND in 22q11DS. There was no significant difference in $D_{2/3}$R BPND between HC and adults with 22q11DS in the OFC and ACC ($F = 1.47$, $p = 0.24$ and $F = 0.40$, $p = 0.53$, respectively; Table 1 and Fig. 3). Results of separate sub-regions of the PFC, OFC, and ACC can be found in the online Supplementary Table S1 and Fig. S3. There was no significant association between $D_{2/3}$R BPND in any of the frontal ROIs ($p > 0.05$) and IQ within the HC group and with IQ or PANSS scores within the 22q11DS group.

Discussion

Here we report the results of the first study investigating frontal dopaminergic neurotransmission in 22q11DS, a genetic syndrome that is considered a valuable model for the study of biomarkers of psychotic disorders and cognitive deficits. As hypothesized, we found lower frontal $D_{2/3}$ receptor BPND in adults with 22q11DS compared with HCs, indicating abnormal frontal DA levels in adults with 22q11DS.

Lower frontal $D_{2/3}$R BPND in 22q11DS

Lower $D_{2/3}$R BPND in frontal brain regions adds to the growing evidence indicating aberrant DA neurotransmission in 22q11DS (Boot et al., 2008, 2010, 2011a; de Koning et al., 2012; Evers et al., 2014; Butcher et al., 2017; van Duin et al., 2018). There are several potential underlying mechanisms that could explain this novel finding.

It is thought that the radiotracer $[^{18}F]$fallypride competes with endogenous DA levels for $D_{2/3}$ receptor binding (Morris et al., 1995; Ceccherini et al., 2012). Lower receptor BPND can therefore be the result of a higher DA concentration in the synaptic cleft, which results in lower BPND due to competition and/or a down-regulation of post-synaptic DA receptor density (Wong et al., 1986; Boot et al., 2011a). This adds to accumulating evidence indicating a hyperdopaminergic state as a general endophenotype of 22q11DS in their young adulthood (Boot et al., 2008; Butcher et al., 2017). In line with current results, a recent PET study in non-psychotic adults with 22q11DS found higher pre-synaptic DA synthesis capacity in striatal brain regions (Butcher et al., 2017). A hyperdopaminergic state could be the result of reduced frontal DA clearance compared with HCs, caused by COMT haplinsufficiency in 22q11DS (Chen et al., 2004; Tunbridge et al., 2006). COMT hemizygosity in 22q11DS is suggested to result in reduced COMT enzyme activity and consequently higher DA levels, especially in the PFC (Tunbridge et al., 2006; Boot et al., 2008; van Beveren et al., 2012), in line with our findings. It has been suggested that the ‘clearance role’ of COMT and the effect of COMT Val/Met genotype in (frontal) DA turnover becomes increasingly important under challenged conditions (Huotari et al., 2002; Yavich et al., 2007), for instance during stress task-induced DA release paradigms (Hernaus et al., 2013). Future studies, possibly using a challenge condition and larger samples, are necessary to elaborate on the role of COMT genotype on frontal DA functioning in 22q11DS.

Furthermore, a chronic exposure to higher endogenous DA could have a toxic effect on dopaminergic neurons and is proposed to precede the onset of DA denervation in 22q11DS which is, amongst others, implicated in Parkinson’s disease (PD) (Goldstein et al., 2014; Butcher et al., 2017). Recent studies indeed show that 22q11DS patients older than 30–40 years have an increased risk for the development of PD (Booij et al., 2010; Butcher et al., 2017), further linking abnormal dopaminergic neurotransmission to 22q11DS.

It is interesting to speculate about the clinical implications of the observed lower frontal $D_{2/3}$R BPND and the proposed hyperdopaminergic state. On the one hand our results may be associated with...
with cognitive impairments often seen in 22q11DS (Oskarsdóttir et al., 2004; Bassett et al., 2005; Biswas and Furniss, 2016; Norkett et al., 2017). Abnormal frontal DA levels may play a role in the induction of cognitive deficits based on the inverted U-shaped curve model (Goldman-Rakic et al., 2000; Gothelf et al., 2008). Thus the lower frontal D_{2/3} BP_{ND} in 22q11DS could be the result of excessive DA levels inducing cognitive deficits, including deficits in memory, attention, and reward processing (Gothelf et al., 2008). Such cognitive domains have previously been shown (using e.g. single-cell recordings and PET imaging) to rely, amongst others, on frontal DA functioning (Goldman-Rakic et al., 2000; Slifstein et al., 2015) and several of these cognitive domains have been found to be impaired in 22q11DS (de Koning et al., 2012; Weinberger et al., 2016; Norkett et al., 2017; van Duin et al., 2018). Future research including a comprehensive cognitive assessment tool is necessary, in order to associate cognitive functioning with frontal DA neurotransmission in 22q11DS.

Abnormal frontal DA levels could furthermore be related to the increased risk for developing psychotic disorders in 22q11DS. Problems in the cognitive domain often occur in psychotic disorders (Green and Nuechterlein, 1999; Nuechterlein et al., 2004).

Moreover, the severity of (primarily) cognitive and negative symptoms of psychotic disorders relying on frontal DA function (Okubo et al., 1997; Abi-Dargham et al., 2002; Slifstein et al., 2015) is likely to be associated with decreased DA release in frontal brain regions (Okubo et al., 1997). Although a frontal hypodopaminergic state is proposed to be related to non-deleted psychosis (Slifstein et al., 2005), we found lower frontal D_{2/3}R BP_{ND} suggestive of a frontal hyperdopaminergic state and/or lower expression of post-synaptic DA receptor density (Wong et al., 1986; Boot et al., 2011a, 2011b) in non-psychotic adults with 22q11DS with (mild) cognitive impairments. This might be explained by the same mechanism as is proposed to result in cognitive dysfunction with the inverted U-shaped curve model (Goldman-Rakic et al., 2000). This model suggests that either too much or too little frontal DA levels induce cognitive deficits, which could also be true for psychosis-related symptoms. It could additionally be explained by previously found differences in DAergic markers in 22q11DS compared with individuals with ultra-high risk (Vingerhoets et al., 2018). Disturbances of the DAergic system in the pathway to psychosis may be different in the 22q11DS population compared with other risk groups.

However, direct evidence for frontal dopaminergic alterations in psychotic disorders is inconsistent and previous findings are inconclusive (Kambeitz et al., 2014). In this study, we found results indicating a hyperdopaminergic state in non-psychotic 22q11DS individuals, suggesting that frontal dopaminergic alterations are present in this group regardless of psychopathology. Future research in a sample including also patients with psychotic symptoms with 22q11DS would be interesting to provide additional insight in the association between psychotic risk and frontal DA functioning.

**Strengths and limitations**

The main strength of this study is the use of a unique patient group with a well-defined genetic syndrome which is a valuable model for the study of biomarkers underlying, among others, cognitive impairments and psychotic disorders. Some limitations of the study should also be taken into account. First, the relatively small sample size of the sample and the use of antidepressant medication in some of the participants. We reanalyzed our main analyses excluding the 22q11DS subjects with medication and replicated our findings, indicating that the results were not affected by medication. Given the challenge of recruitment of (medication-naive) participants, the 22q11DS sample (size) could be considered representative, also in light of previous studies using similar paradigms (Hernaus et al., 2013; Kasanova et al., 2017; van Duin et al., 2018).

Secondly, given the well-known association between smoking (status) and DA function (Mansvelder and McGehee, 2000), we reanalyzed our main analyses excluding the HC subjects that were habitual cigarette smokers and replicated our findings, indicating that the results were not affected by smoking status.

Additionally, the design of the scanning protocol may also have affected the results, and should be taken into consideration in future research. For the analysis of ‘relative resting state’ DA levels, from the original protocol, the sensorimotor control and baseline condition were analyzed, without the experimental condition (designed to induce reward-related DA release) (Kasanova et al., 2017, 2018; van Duin et al., 2018). This design is necessary to detect reliable task-induced changes on the [18F]fallypride uptake (Vernakelen et al., 2011). A sensorimotor control task was used to control for sensorimotor influence on the experimental reward task condition and to keep subjects awake, in order to prevent unpredictable head movement. Although the subjects were well instructed before the sensorimotor control task (Fig. 1), the task might have influenced and elicited (sensorimotor-induced) DA release in frontal brain regions. However, this would have been the case for both the control and the 22q11DS group, and there is no evidence, to the best of our knowledge, to suggest that 22q11DS confers a different DA release to sensorimotor tasks compared with controls.

Furthermore, lower D_{2/3}R BP_{ND} was found in the PFC and the anterior cingulate gyrus, however only the difference in the anterior cingulate gyrus survived the Bonferroni correction. Although D_{2/3}R BP_{ND} seemed also lower in the OFC and ACC in 22q11DS compared with controls, this difference failed to reach significance. This could be due to a power issue and in increased sample sizes it is expected to find significant differences in these regions as well. More research is necessary to further explain the absence of significant differences in the OFC and ACC.

**Conclusion**

This study is the first to demonstrate lower frontal dopamine D_{2/3} receptor binding in adults with 22q11DS, which may represent a hyperdopaminergic state in frontal brain areas. This could be the result of haplo-insufficiency of COMT in these patients, and may play a role in their increased risk for developing cognitive impairments and psychotic disorders.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S003329171900062X.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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