Abnormal Cortical Activation During Response Inhibition in 22q11.2 Deletion Syndrome

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Abstract: 22q11.2 deletion syndrome (22q11.2DS) is a well-known genetic risk factor for schizophrenia. The catechol-*O*-methyltransferase (COMT) gene falls within the 22q11.2 minimal critical region of the deletion. Brain activity, as measured by functional magnetic resonance imaging (fMRI) during a Go/NoGo, response inhibition task was assessed in adolescents with 22q11.2DS ($n = 13$), typically developing (TD) controls ($n = 14$), and controls with developmental disability (DD, $n = 9$). Subjects with 22q11.2DS were also genotyped for the *COMT* Met/Val polymorphism. Groups did not differ on task performance. However, compared to both control groups, the 22q11.2DS group showed greater brain activation within left parietal regions. Comparison of brain activation between 22q11.2DS Met and Val subgroups revealed significantly increased activation (Met>Val) in the cingulate but not the dorsolateral prefrontal cortex. These preliminary findings suggest that adolescents with 22q11.2DS compensate for executive dysfunction via recruitment of parietal regions. Further, the *COMT* Met subgroup of 22q11.2DS may recruit additional cingulate activation for tasks requiring attention and inhibition. 22q11.2DS is a unique model for learning about the deleterious effects of decreased dosage of the *COMT* gene on brain function. *Hum Brain Mapp 28:533–542, 2007.* ©2007 Wiley-Liss, Inc.

Key words: velocardiofacial syndrome; schizophrenia; functional MRI; imaging genetics; COMT; parietal lobe; cingulate

INTRODUCTION

The 22q11.2 deletion syndrome (22q11.2DS), also known as DiGeorge/velocardiofacial syndrome is caused by a microdeletion on chromosome 22 and occurs in at least 1:5000 live births [Botto et al., 2003]. The syndrome has more than 180 possible physical manifestations, the most prominent of which are congenital anomalies of the palate, heart and great vessels and typical facial features (the velocardiofacial manifestations), hypocalcaemia, and T-cells deficiency (the DiGeorge manifestations) [Kirkpatrick and DiGeorge, 1968; Shprintzen, 2000]. In addition to the

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physical phenotype, there is a high rate of psychiatric morbidity in subjects with 22q11.2DS and most subjects with 22q11.2DS suffer from learning disabilities [Feinstein et al., 2002; Gothelf et al., 2004; Murphy et al., 1999; Swillen et al., 1997]. There is an overall delay in cognitive development in subjects with 22q11.2DS with an average overall IQ in the range of 70–85 [Swillen et al., 1997].

The 22q11.2DS is a promising model to learn about risk factors for the evolution of schizophrenia. This is because up to one third of individuals with this condition develop schizophrenia or related psychotic disorders, making 22q11.2DS the most common known risk factor for development of psychosis [Gothelf et al., 2005; Murphy et al., 1999]. In addition, the psychiatric characteristics and cognitive deficits of 22q11.2DS schizophrenia are very similar to schizophrenia in non-22q11.2DS [Bassett et al., 2003; van Amelsvoort et al., 2004].

Similar to subjects with idiopathic schizophrenia, subjects with 22q11.2DS are especially weak in areas of executive functioning, maintenance of attention, and visuo-spatial processing [Bish et al., 2005; Sharma and Antonova 2003; Sobin et al., 2004; Woodin et al., 2001]. Also, similar to subjects with idiopathic schizophrenia, children with 22q11.2DS show deficient startle inhibition as measured by the prepulse inhibition [Sobin et al., 2005]. Several studies have investigated cognition in subjects with 22q11.2DS. Relative to individuals with 22q11.2DS who do not manifest schizophrenia, persons with 22q11.2DS and schizophrenia demonstrate worse performance in core cognitive domains typically associated with idiopathic schizophrenia including attention, spatial working memory, visual recognition, and social cognition [Chow et al., 2006; van Amelsvoort et al., 2004].

The purpose of the present study was to elucidate the abnormal neural processing underlying executive dysfunction and cognitive disinhibition in individuals with 22q11.2DS [Bish et al., 2005; Sobin et al., 2004]. These deficits are of special importance, as they also seem to be cognitive endophenotypes of schizophrenia [Gottesman and Gould 2003]. For the study described here, we chose to use a cognitive task with low-demand, a Go/NoGo task, so as to be able to match subjects with 22q11.2DS to controls on task performance. Obtaining appropriate levels of compliance from children with developmental disability and mental retardation for functional magnetic resonance (fMRI) studies is a complex endeavor. This may explain why there are no published fMRI studies evaluating executive function in 22q11.2DS to date. Though subject groups were matched in terms of task performance, we predicted that subjects with 22q11.2DS would demonstrate higher activation of brain regions typically involved in the Go/NoGo task, reflecting reduced efficiency of neural processing.

The second purpose of the study was to compare activation of the prefrontal cortex (PFC) during performance of the Go/NoGo task between the 22q11.2DS catechol-*O*-methyltransferase (*COMT*) Met and Val subgroups. The *COMT* gene, one of the major genes hypothesized to mediate prefrontal cognitive deficits in schizophrenia [Egan et al., 2001], is within the 22q11.2 critical deletion region [Maynard et al., 2003]. Since all subjects with 22q11.2DS are hemizygous for *COMT*, genotypic variation for this gene affords the opportunity to learn about the effect of extreme COMT deficiency on PFC activation. Based on our previous findings of association between the *COMT* Met allele, cognitive decline, and the emergence of psychotic symptoms [Gothelf et al., 2005], we predicted that 22q11.2DS Met hemizygotes would require greater brain activation than *Val* hemizygotes, within the cingulate and dorsolateral PFC (DLPFC), to achieve comparable levels of task performance. We limited the Met/Val comparison to these two PFC regions of interest (ROIs) as previous studies with non-22q11.2DS subjects have shown that the *COMT* Met/Val genotype affects brain activation in these brain areas during executive function tasks [Blasi et al., 2005; Egan et al., 2001].

SUBJECTS AND METHODS

Participants

Thirty-six subjects comprising three groups participated in the study. These included 13 subjects with 22q11.2DS, 14 typically developing (TD) subjects, and 9 subjects with idiopathic developmental disabilities (DD). Twenty subjects with 22q11.2DS were initially scanned, but seven were excluded because of severe motion. Subjects were recruited as part of the Stanford Center for Interdisciplinary Brain Sciences Research (CIBSR) longitudinal neuroimaging studies of 22q11.2DS and other neurogenetic/neurodevelopmental conditions. The TD and DD control groups were recruited by advertisement on our website (http://cibsr.stanford.edu), local newspapers, online parent groups, and from local schools. The presence of the 22q11.2 microdeletion was confirmed by fluorescence in situ hybridization (FISH) with probes D0832 (COMT) and N48C12 (D22S264) [Karayiorgou et al., 1995]. Controls were not tested for the presence of chromosomal or metabolic abnormalities.

As can be seen in Table I, the three groups were similar in age, ethnicity, handedness, and gender distribution. On analysis of variance (ANOVA), the three groups significantly differed in full scale IQ (FSIQ). On Sheffe posthoc pairwise comparisons, the FSIQ of the TD group (mean ± SD, 122.2 ± 12.8) was significantly higher ($P < 0.001$) than the 22q11.2DS (74.5 ± 18.9) and DD (61.2 ± 10.1) groups. There was no significant difference in FSIQ between the 22q11.2DS and DD groups ($P = 0.13$). All subjects underwent fMRI while performing the Go/NoGo task. Three participants were treated at the time of the study with risperidone (two from the 22q11.2DS group and one from the DD group) and two subjects from the DD group were treated with stimulants. Three subjects from the 22q11.2DS group had a psychotic disorder (two schizoaffective disor-

TABLE I. Demographic characteristics and behavioral performance during the Go/NoGo and Go conditions in the 22q11.2DS, TD, and DD groups

	22q11.2DS (n = 13)	TD (n = 14)	DD (n = 9)	Statistics (df = 2, 33)
Age	17.8 (3.5)	17.2 (3.4)	18.1 (4.8)	$F = 0.2$, $P = 0.86$
Males/females	8/5	7/7	4/5	$\chi^2 = 0.7$, $P = 0.71$
Full-scale IQ[a]	74.5 (18.9)	122.2 (12.8)	61.2 (10.1)	$F = 57.2$, $P < 0.001$
Ethnicity				
Caucasian	11	12	6	$\chi^2 = 1.7$, $P = 0.78$
Asian		1	1	
Hispanic	1	1		
Mixed race	1		2	
Handedness				
Right/left	12/1	14/0	8/1	$\chi^2 = 1.5$, $P = 0.48$
Hit rate	86.8 (23.6)	96.3 (5.1)	89.5 (18.7)	$F = 1.8$, $P = 0.17$
False alarms rate	13.2 (12.1)	8.4 (5.1)	15.3 (14.7)	$F = 1.3$, $P = 0.29$
RT to Go trials	504.4 (84.4)	504.4 (111.7)	584.8 (115.4)	$F = 1.9$, $P = 0.17$
RT to NoGo errors	411.8 (127.3)	417.7 (139.9)	532.8 (210.2)	$F = 1.4$, $P = 0.26$

[a] On Scheffe posthoc pairwise comparisons, TD group had significantly higher full-scale IQ than 22q11.2DS and DD groups.

der and one schizophrenia). Written informed consent was obtained from the subjects after the nature of the experimental procedures was explained. In case of minors, assent was obtained from the subjects and written consent from their parents. The study was approved by the Stanford University Institutional Review Board.

Genotyping

Blood was drawn and genotypes determined only for the 22q11.2DS group and their available parents. DNA was extracted from blood leukocytes by standard techniques (Puregene, Gentra, MN). The Val108/158Met polymorphism (rs165688) was genotyped by PCR and restriction digestion according to standard techniques and was determined by NlaIII digestion (NlaIII+ = Met, NlaIII− = Val) [Lachman et al., 1996].

Neuropsychological Assessment

General cognitive level was assessed with the Wechsler Intelligence Scale for Children, 3rd edition (WISC III) [Wechsler, 1991] for subjects 17 years and younger and the Wechsler Adult Intelligence Scale, 3rd edition (WAIS III) [Wechsler 1997] for subjects older than 17 years.

Task

The experimental task consisted of two alternating conditions: Go and Go/NoGo as described [Hoeft et al., 2007, same issue]. Throughout both conditions, subjects viewed a series of letters once every 2 s and responded with a key press, using the forefinger of the right hand, to every letter except the letter "X," to which they were instructed to withhold response. In the Go (control) condition, subjects were presented a random sequence of letters other than the letter "X." In the Go/NoGo (experimental) condition, subjects were presented with the letter "X" 50% of the time. The entire task lasted a total of 372 s and consisted of 12 alternating 26-s periods of Go and Go/NoGo conditions flanked at the beginning and end by 30-s rest periods during which the subject passively viewed a blank screen. The beginning of each period consisted of a 2-s instruction alerting the subject to the present task condition. The hit rates, false alarm rates, and reaction times (RT) to Go trials during each condition were compared between groups using analyses of variance.

Image Acquisition

All imaging and imaging-related procedures were conducted at the Lucas Center for Magnetic Resonance Spectroscopy and Imaging, Stanford University, on a 1.5T General Electric Signa whole-body MR system (GE Medical Systems, Milwaukee, WI). A total of 186 whole-brain volumes were collected on 18 axial-oblique slices (6 mm thick, 1 mm skip) prescribed parallel to the intercommissural (AC-PC) line, using a T2*-weighted gradient echo spiral pulse sequence [Glover and Lai 1998] sensitive to blood oxygen level-dependent (BOLD) contrast with the following acquisition parameters: echo time (TE) = 30 ms, repetition time (TR) = 2000 ms, flip angle = 89, FOV = 24 × 24, acquisition matrix = 64 × 64, voxel size = 3.75 × 3.75 × 6 mm. Participants' heads were immobilized using a custom-built head stabilizer to ensure minimal head movement during the scan. All subjects participated in a mock scan to familiarize them with the scanning procedures.

fMRI Preprocessing

fMRI image processing and statistical analyses were performed using Statistical Parametric Mapping software (SPM2) (Wellcome Department of Cognitive Neurology,

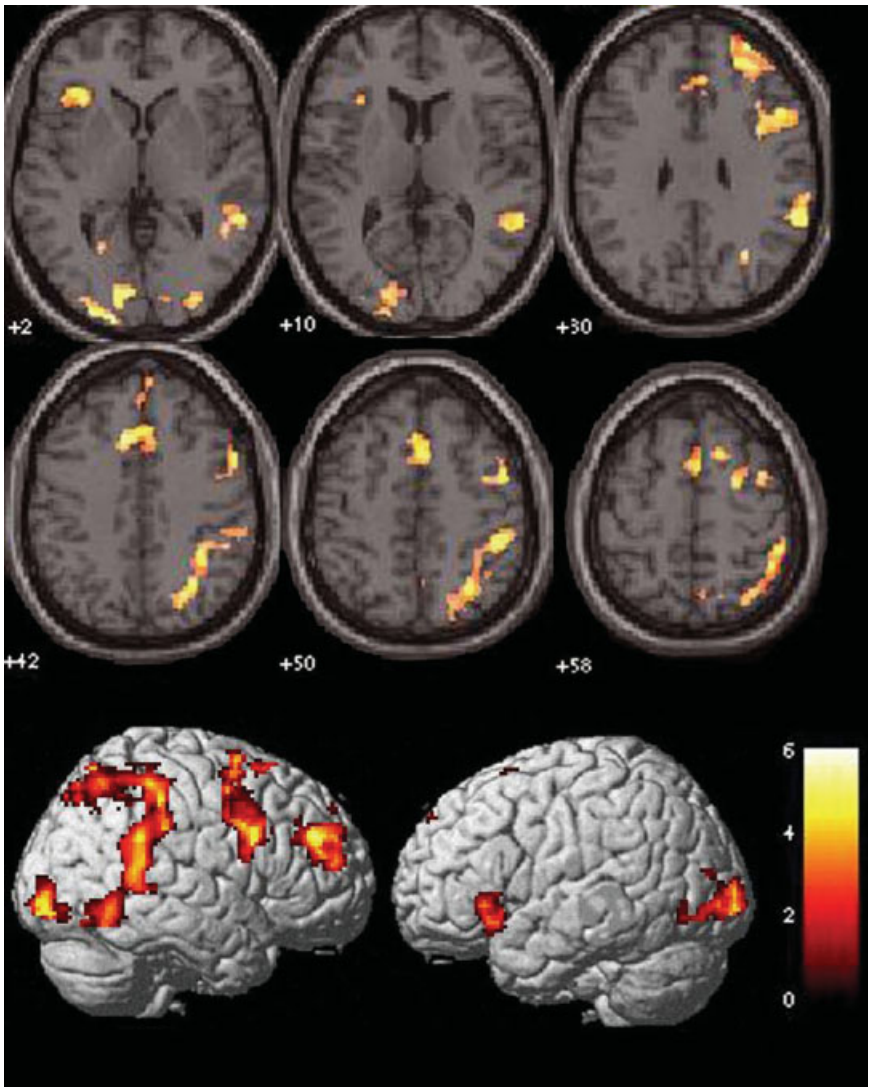

Figure 1.
Brain activation patterns across 22q11.2DS, TD and DD groups.

London, UK). After scanning, images were reconstructed and realigned to the reference functional volume. Sessions were then normalized using the mean functional volume resampled to 2 × 2 × 2 mm voxels in Montreal Neurological Institute (MNI) stereotaxic space and smoothed in three-dimensional space with a Gaussian filter (4 mm full width half-maximum, FWHM).

Data Analysis

Behavioral scores on the Go/NoGo task between 22q11.2DS, TD, and DD groups were compared by using ANOVAs with Scheffe posthoc pairwise comparisons. Behavioral scores between 22q11.2DS *COMT* genotype subgroups were compared using Mann-Whitney *U* test.

Each subject's fMRI data were high pass filtered at 120 s, globally scaled, and analyzed using a fixed effects model to reveal those areas that showed greater activation during the Go/NoGo than the Go task conditions (Go/NoGo contrast). A whole brain analysis using one-sample *t*-test combining all subjects was performed to examine regions that showed a significant effect for the Go/NoGo contrast in the three groups. We then performed group analyses using a random effects model. Our assumption was that 22q11.2DS subjects would show less efficient brain activation while performing the Go/NoGo task, beyond that associated with general cognitive impairment. We therefore directly compared the 22q11.2DS with TD and DD groups. Further, we included four nuisance variables: IQ, d', antipsychotics, and stimulants intake. Significant clusters of activation were determined by using the joint-expected probability distribution with height ($P < 0.01$) and extent ($P < 0.01$) thresholds corrected at the whole-brain level [Poline et al., 1997]. Confirmatory ANOVAs comparing the extracted contrast estimates among the three groups were also performed.

TABLE II. Regions activated during the response inhibition task in the total study sample (n = 36, P < 0.01 corrected)

Region	Talairach coordinates (x, y, z)	Maximum T value	Cluster size (voxels)
Cingulate, medial frontal and R superior frontal gyri (BA 32, 8, 6)	−8, 21, 38	5.40	1798
R superior frontal gyrus (BA 9, 10)	32, 55, 21	5.70	702
R inferior and middle occipital gyri (BA 18)	28, −90, −4	6.03	397
Left inferior frontal gyrus, insula (BA 47, 13)	−36, 27, −1	5.10	362
R inferior and superior parietal gyri (BA 7, 40)	59, −39, 28	5.78	2496
L cuneus and middle occipital gyrus (BA17, 18)	−20, −97, 1	5.79	767

SPMs were overlaid onto the SPM2 high-resolution T1 individual brain for viewing. Coordinates of activation were converted from MNI to Talairach space using the mni2tal function (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml). Brain regions were then identified from these x, y, z coordinates using the Talairach Daemon (Research Imaging Center, University of Texas Health Science Center in San Antonio (RIC, UTHSCSA, TX) and confirmed with the Talairach atlas [Talairach and Tournoux 1988].

To further investigate the effect of *COMT Val/Met* genotype on brain activation during the Go/NoGo task, we compared Go/NoGo contrasts (NoGo > Go) between the 22q11.2DS *Met* and *Val* subgroups by employing region of interest (ROI) analyses restricted to the cingulate gyrus [Brodmann Area 24 and 32, (BA24/32)] and DLPFC (BA9/46, P < 0.05 small volume correction, SVC). The ROIs were created using the WFU PickAtlas 1.02 [Maldjian et al., 2003].

RESULTS

Go/NoGo Behavioral Scores

Table I shows the scores of the 22q11.2DS, TD, and DD groups on the Go/NoGo task. All subjects with usable data were included in the analysis, that is, subjects were not intentionally selected to match on task performance. Yet, ANOVA showed that there were no significant differences among the three groups on task parameters including hit rate, false alarms, RT to the Go trials and RT to the NoGo errors. In the 22q11.2DS group, seven were *COMT* Val and six were *COMT* Met hemizygotes. There were no significant differences within the 22q11.2DS Met vs. Val subgroups on any of the demographic parameters including FSIQ scores, gender, ethnicity, and handedness distribution or performance on the Go/NoGo task including hit and false alarm rates, RT on the Go trials, and NoGo errors (all P values ≥ 0.17).

Functional MRI

Brain activation common to all groups

Whole brain analyses combining all subjects revealed significant activation in several brain regions ($P < 0.01$ corrected). These areas, including the DLPFC and ventrolateral PFC (VLPFC), medial prefrontal, cingulate and parietal regions, were consistent with past findings of response inhibition [Durston et al., 2002; Menon et al., 2001; Wager et al., 2005] and are presented in Figure 1 and Table II.

Effect of 22q11.2 deletion syndrome

Direct comparisons between groups revealed one large cluster in the left superior and inferior parietal lobules that showed significantly greater activation in the 22q11.2DS group compared with the TD and DD groups while performing the Go/NoGo task ($P < 0.01$ corrected) (Fig. 2 and Table III). There were no regions that showed significantly greater activation in the TD and DD groups compared with the 22q11.2DS group.

To confirm that greater activation of the left parietal region observed in 22q11.2DS is not driven by only one of the control groups, we extracted contrast estimates, i.e., linear combination of beta values, from this region. Contrast estimates were compared between 22q11.2DS, TD and DD groups. On ANOVA, a main effect of group was found ($F = 8.5$, $P = 0.001$, partial $Z^2 = 0.34$). On Scheffe post hoc pairwise comparisons, the 22q11.2DS group showed greater activation than TD ($P = 0.006$) and DD groups ($P = 0.005$, see graph in Fig. 2).

Effect of COMT Met/Val polymorphism

Within the 22q11.2DS group, there was significantly greater activation in the *COMT* Met subgroup compared with the *COMT* Val subgroup in the cingulate gyrus [BA24 (x, y, z: −4, 5, 31); cluster size: 48 voxels; $t = 3.6$, $P < 0.01$, effect size (Cohen's d) = 1.6; Fig. 3]. There were no significantly greater activations in the *Val* compared to the *Met* subgroup. There was also no significant effect of genotype on activation in the DLPFC (BA9/46) ROI.

DISCUSSION

Because of the strong association with schizophrenia, 22q11.2DS has been the focus of intensive research, includ-

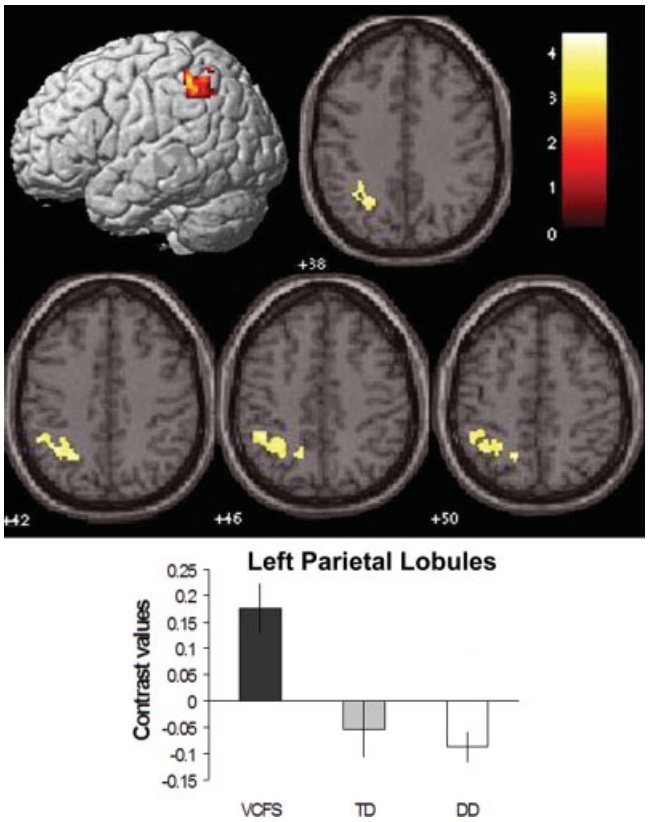

Figure 2.
A cluster that includes regions of left superior and inferior parietal lobules showed significantly greater activation in 22q11.2DS vs. the TD and DD control groups during the Go/NoGo vs. Go condition.

ing several structural brain imaging studies [see Eliez and van Amelsvoort 2005 for review]. In contrast, till date, there has been only one functional brain imaging publication on 22q11.2DS, in which mathematical performance was the focus [Eliez et al., 2001]. Functional MRI studies in subjects with 22q11.2DS can potentially provide key information for identifying aberrant neural function underlying cognitive and psychiatric symptoms in affected individuals. In turn, aberrant profiles of brain function can serve as candidate endophenotypes associated with the strong predisposition of subjects with 22q11.2DS to develop psychotic disorders.

As hypothesized, we found that relative to the TD and DD groups, subjects with 22q11.2DS showed significantly greater activation in a large cluster within the left parietal lobe. In contrast, the control groups did not show greater activation in any brain region compared with subjects with 22q11.2DS. The fact that the 22q11.2DS group's behavioral scores on the Go/NoGo task were similar to controls indicates that individuals with this condition have the capacity to compensate for less efficient neural processing for simple executive functioning tasks like a Go/NoGo paradigm. To our knowledge, the performance of individuals with 22q11.2DS on a Go/NoGo task had not been previously reported. However, other related cognitive deficits have been documented in this population, including deficits in various aspects of executive functioning [Woodin et al., 2001], visual attention [Sobin et al., 2004], working memory [Baker et al., 2005] and maintenance of attention [Woodin et al., 2001]. It is also possible that DD controls compensate for less efficient cognitive functioning by recruiting other brain regions. However, our study could not test this hypothesis because of the small number of subjects in this comparison group.

As shown in Figure 2, BA7/40 in the left parietal lobe was activated only in the 22q11.2DS group and not in the TD or DD control groups. Aberrant parietal activation in 22q11.2DS relative to controls is in line with the accumulating evidence that parietal deficits are at the core of the 22q11.2DS phenotype. Structural imaging data indicate that children and adolescents with 22q1.2DS have reduced parietal grey matter and white matter volumes even after controlling for their reduced cortical volumes [Campbell et al., 2006; Eliez et al., 2000; Kates et al., 2001]. Furthermore, studies indicate that parietal dependent cognitive functions, including visuo-spatial and numerical abilities, are especially deficient in children with 22q11.2DS [Simon et al., 2005]. As recently proposed [Bish et al., 2005], parietal dysfunction in individuals with 22q11.2DS may contribute to overall executive dysfunction in affected individuals through impairment of a person's ability to orient visual cues. In line with the results of our study, a study using the Go/NoGo task found that individuals with schizophrenia had increased brain activity compared to controls in the region of the intraparietal sulcus bilaterally [Laurens et al., 2003]. Other structural and functional studies in schizophrenia suggest that parietal abnormalities may exist early in the course of the disease and perhaps even before its onset [Job et al., 2005; Whalley et al., 2006].

TABLE III. Regions showing greater activation in 22q11.2DS subjects than controls for the Go/NoGo vs. Go contrast[a]

Region	TAL:*x*	TAL:*y*	TAL:*z*	*T* score
Left superior/inferior parietal lobules (BA 7/40)	−26, −28, −36	54, −50, −50	40, 54, 41	4.48

[a] No. of voxels: 573.

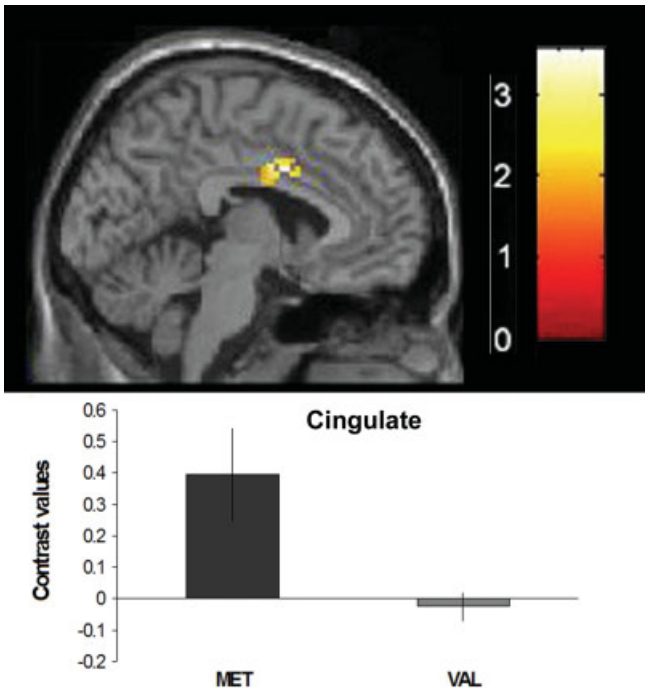

Figure 3.
Effect of *COMT* genotype on cingulate gyrus (BA24/32) activation during the Go/NoGo vs. Go condition in subjects with 22q11.2DS. A cluster within the cingulate gyrus (BA24) with greater activation in the *COMT* Met vs. Val subgroups is shown.

Taken together, parietal dysfunction is a candidate endophenotype that may be associated with the development of psychosis in individuals with 22q11.2DS. It should be noted that while there is certainly some overlap between the neuroanatomical and cognitive deficits associated with 22q11.2DS and those associated with idiopathic schizophrenia, the patterns are not identical. For example, in comparison to typically developing controls, frontal lobe volume in 22q11.2DS tends to be preserved while it is decreased in volume in idiopathic schizophrenia [Eliez et al., 2000]. Similarly, though verbal memory is impaired in patients with idiopathic schizophrenia, there are no differences in this cognitive function between 22q11.2DS subjects with and without schizophrenia [van Amelsvoort et al., 2004].

To test the second hypothesis regarding differences between *COMT* Met and Val hemizygotes within the 22q11.2DS group, we chose to focus on two key prefrontal regions for executive control, the DLPFC and the cingulate. The cingulate (BA24/32) ROI was chosen as healthy subjects were observed to show a robust effect of *COMT* Met/Val polymorphism on brain activation within this region during performance of an attentional control task [Blasi et al., 2005]. This attentional control task is similar to the Go/NoGo task used in the present study with respect to reliance on attention and conflict monitoring. The location of the cluster in the cingulate gyrus of 22q11.2DS subjects that showed greater activation in the Met compared to the Val subgroup was overlapping with the cluster identified in the Blasi et al. [2005] study. As shown in Figure 3, the cluster of activation in BA24 occurred only in the 22q11.2DS Met and not in the 22q11.2DS Val carriers, suggesting that greater cingulate recruitment is required in Met hemizygotes when performing a response inhibition task. Although the DLPFC was activated during the Go/NoGo performance in the 22q11.2DS group, the *COMT* genotype did not affect activation of this region. Similarly, in Blasi et al. [2005], though the DLPFC and additional cortical regions were activated during the attentional control task, *COMT* genotype was observed to affect degree of activation only in the cingulate gyrus. Together, these findings suggest that the *COMT* Met/Val polymorphism particularly affects attentional control and response inhibition via the cingulate gyrus as opposed to the DLPFC.

The segment of the cingulate gyrus that was significantly more activated on the Go/NoGo task in Met vs. Val hemizygote 22q11.2DS subjects receives abundant dopaminergic projections [Seamans 2004]. In the Blasi et al. [2005] study, Val/Val subjects showed greater (less efficient) cingulate gyrus activation than Met/Met subjects. In the present study, 22q11.2DS Met hemizygotes showed greater cingulate gyrus activation than Val hemizygote subjects. The apparent opposing effect of *COMT* Met/Val polymorphism in 22q11.2DS and non-22q11.2DS subjects can best be explained according to the known inverted-U shape relation that exists between prefrontal cortical dopamine levels and cognitive functioning [Goldman-Rakic et al., 2000]. Consequently, too little or too much prefrontal D_1 receptor stimulation is associated with less optimal cognitive function. Non-22q11.2DS hemizygotes for Val have too much COMT activity and thus have less than optimal prefrontal dopamine levels; whereas 22q11.2DS Met hemizygotes are putatively in extreme shortage of COMT activity and hence are thought to have too high prefrontal dopamine levels. In a recent longitudinal study of group of children with 22q11.2DS followed to adolescence we found evidence supporting the effect of the inverted-U shape model on cognitive function in 22q11.2DS. During adolescence, the subgroup of 22q11.2DS children with the Met allele declined more in VIQ and expressive language abilities and developed more severe psychotic symptoms than the subgroup with the Val allele [Gothelf et al., 2005].

In the present study, functional imaging data were acquired from most subjects at the second time point of our longitudinal study. Of note, other cross-sectional studies in 22q11.2DS have presented conflicting results regarding the effect of *COMT* Met/Val genotype on cognitive functioning [Bearden et al., 2004; Glaser et al., 2006]. In our cohort, the effect of the *COMT* Met/Val polymorphism was only revealed by longitudinal analysis [Gothelf et al., 2005]. In other words, though there was no significant difference in IQ between the *COMT* Met and Val carriers at Time 2, the decline in VIQ among carriers of the *COMT* Met subgroup was significant compared to the *COMT* Val subgroup.

Abnormal activation of the cingulate gyrus, during performance of response conflict and response inhibition tasks, has been observed in individuals with idiopathic schizophrenia [Kerns et al., 2005; Snitz et al., 2005]. Also, activation of the cingulate in individuals with schizophrenia appears to be sensitive to changes in dopamine levels [Dolan et al., 1995]. Thus, abnormal activation of the cingulate gyrus in 22q11.2DS *COMT* Met carriers may represent a biological marker for increased risk for psychosis.

In healthy subjects, the *COMT* genotype affects PFC response to medication-induced increase in brain dopamine levels. Mattay et al. [2003] observed that administration of amphetamine improved working memory performance of Val/Val healthy subjects while causing deterioration of cognitive performance in Met/Met subjects. These effects were also noted on brain activity during a task where prefrontal activation was observed to be significantly greater in the Met/Met than in the Val/Val group. It could be hypothesized that like healthy subjects treated with amphetamine, the *Met* subgroup of 22q11.2DS subjects also experience a hyperdopaminergic condition, that is, both are on the down slope of the inverted-U shape of dopamine level in relation to cognitive functioning. Thus, in both situations we observe less efficient cognitive functioning and greater cingulate activation. The lack of *COMT* Val158Met effect on DLPFC activation in the present study is likely to be related to the task chosen, that is, response inhibition, which is not a DLPFC-specific cognitive task.

The data presented here provide further support for the hypothesis that *COMT* genotype influences neural function in 22q11.2DS. However, other (non-imaging) studies did not find a clear association between *COMT* genotype and either neuropsychiatric [Bassett et al., 2007] or cognitive deficits [Glaser et al., 2006] in affected individuals. Taken as a whole, these findings are likely to reflect differences in studying behavior at more than one level of scientific inquiry (i.e. fMRI vs. IQ) as well as potential interactive effects between the *COMT* gene and other genes from the 22q11.2 deletion region. In particular, it is likely that halpoinsufficeincy for more than one gene contributes to cognitive and neuropsychiatric outcome in persons with 22q11.2DS. One major candidate for such interaction is the proline-dehydrogenase (*PRODH*) gene. The *PRODH* gene is within the 22q11.2 deletion region and codes for the proline dehydrogenase enzyme. In mice knocked-out for *PRODH* there is an upregulation of *COMT* expression, indicating a homeostatic response to enhanced dopaminergic signaling in the frontal cortex that emerges secondary to PRODH deficiency [Paterlini et al., 2005]. In line with these animal findings, a recent study reported that within the overall 22q11.2DS population, those subjects with hyperprolinemia and the *COMT* Met allele were 3 times more likely to have a psychotic disorder [Raux et al., 2007].

In summary, we found abnormal brain activation in parietal regions in subjects with 22q11.2DS performing a response inhibition task. The role of the *COMT* genotype on cognitive performance and brain activation requires further study with a larger sample of subjects and with other cognitive tasks assessing prefrontal functioning. In particular, the effect of *COMT* genotype on DLPFC function in 22q11.2DS should be evaluated using more DLPFC-specific experiments such as N-Back working memory tasks. Future longitudinal studies should also evaluate whether abnormal brain activations (e.g., in parietal regions) predict the later development of psychotic disorders in 22q11.2DS.

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