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Relationship of *DAT1* and adult ADHD to task-positive and task-negative working memory networks

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Abstract

Alterations in working memory, default-mode network (DMN), and dopamine transporter have all been proposed as endophenotypes for Attention-Deficit Hyperactivity/Disorder (ADHD). Despite evidence that these systems are interrelated, their relationship to each other has never been studied in the context of ADHD. In order to understand the potential mediating effects of task-positive and task-negative networks between *DAT1* and diagnosis, we tested effects of genotype and diagnosis on regions of positive and negative BOLD signal change (as measured with fMRI) in 53 adults with ADHD and 38 control subjects during a working memory task. We also examined the relationship of these responses to ADHD symptoms. Our results yielded four principal findings: 1) association of 9R with adult ADHD, 2) marginal *DAT1* association with task-related suppression in left medial PFC, 3) marginal genotype \times diagnosis interaction in the dorsal anterior cingulate cortex, and 4) correlation of DMN suppression to ADHD symptoms. These findings replicate the association of the 9R allele with adult ADHD. Further, we show that DMN suppression is likely linked to *DAT1* and to severity of inattention in ADHD. DMN may therefore be a target of *DAT1* effects, and lie on the path between the gene and inattention in ADHD.

Keywords

fMRI; default-mode network; attention

1. Introduction

The “default-mode network” (DMN) describes a functionally connected set of brain regions that is more active at rest than during externally-oriented cognitive tasks (Buckner et al., 2008). It is a “task-negative” network, showing negative signal change during task as compared to resting baseline conditions. Further, as demands for attention to external stimuli increase, activation of DMN decreases and activation of “task-positive” networks increase, suggesting that resources are being allocated away from DMN and towards brain regions that support attention to task. Results from several studies suggest that deficits in attention to task can be linked to inadequate suppression of DMN during task performance (Weissman et al., 2006; Li et al., 2007; Eichele et al., 2008; Kelly et al., 2008). The behavioral consequences have been reflected in increased reaction time (RT) variability (Kelly et al., 2008), and self-reported mind wandering (Mason et al., 2007). Even on a trial-by-trial basis, reduction in task-related suppression of DMN regions has been found to temporally precede individual responses characterized by longer RTs (Weissman et al., 2006).

Working memory (WM) describes the set of cognitive processes that allow internal representations of stimuli in their absence, acting as a temporary workspace for incoming information to be held in mind, manipulated, or associated with memories that are accessed from long-term storage. WM is critical for higher order cognition as it allows active representations of information guiding conduct (e.g. rules) as well as providing a domain in which precepts can be considered against past emotions and experiences (Baddeley, 2003; D’Esposito, 2007).

Neuroimaging studies show that across WM tasks, a robust network of lateral frontal, posterior parietal, and anterior cingulate cortices are activated during working memory processes (Wager & Smith, 2003; Owen et al., 2005). Likewise, DMN is suppressed during

working memory tasks (Whitfield-Gabrieli et al., 2009; Anticevic et al., 2010). Further, WM tasks are sensitive to DMN interference, with decreased task-related suppression predicting poorer performance in healthy adult subjects as well as participants at genetic risk for schizophrenia (Whitfield-Gabrieli et al., 2009; Anticevic et al., 2010). Therefore it is likely that adequate regulation of both “task-positive” and “task-negative” is necessary for successful performance. In a group of children with Attention-Deficit/Hyperactivity Disorder (ADHD), Fassbender et al (2009) found that task-related suppression of DMN during a serial addition task was decreased in ADHD subjects compared to controls, and that lack of suppression was associated with increased attentional fluctuations. These findings support the “Default-Mode Interference Hypothesis” (Sonuga-Barke & Castellanos, 2007), which maintains that ADHD-related inattention may be explained at least partially by periodic intrusions of DMN into cognitive and brain processes supporting externally-oriented tasks.

Although there is abundant support for a key role of dopamine in WM performance (Brozoski et al., 1979), it has not been tested whether these effects might be at least partially mediated via task-negative networks. However, mounting evidence supports a role for dopamine in DMN regulation, and specifically that the dopamine transporter protein (DAT) may be an important regulator of task-related suppression. In a recent Positron Emission Tomography/functional Magnetic Resonance Imaging (PET-fMRI) study, Tomasi et al (2009) found that DAT negatively predicted task-related suppression, in that adults with higher DAT binding showed less DMN suppression during a visual attention task. In addition, results from a pharmacological fMRI study of psychostimulants (e.g. methylphenidate/d-amphetamine), which work at least partially by blocking DAT function, showed that administration of the drug reversed a lack of task-related suppression that was found in children with ADHD at a medication naive baseline (Peterson et al., 2009).

Several imaging genetics studies have shown a relationship between a variable number tandem repeat (VNTR) in the 3' untranslated region (UTR) of the gene that codes for DAT (*DAT1* 3'-UTR VNTR) and task-positive regions supporting WM. For example, the polymorphism has been shown in several studies of healthy adults by Bertolino et al (2006; 2008; 2009) and in healthy children by Stollstorff et al (2010) to have an effect on lateral prefrontal cortex activity during N-back tasks. The direction has been consistent throughout these reports: homozygosity for the 10-repeat allele predicts less activity in task-positive regions supporting WM. The effect of this gene variant on task-negative regions suppressed during working memory has not been investigated.

The effect of the *DAT1* 3'-UTR VNTR on brain activity in ADHD has been less consistent, with only three fMRI studies published to date (see Durston, 2010 for review). Inconsistencies are found in the left dorsal anterior cingulate cortex (dACC), where Bedard et al (2010) found that the 10R allele was associated with increased activation in children with ADHD, while Brown et al (2010) found that it was associated with decreased activity in this region in a sample of adults with ADHD. Further, while Durston et al (2008) found that the 10R/10R genotype predicted more activity in the cerebellar vermis of boys with ADHD, Brown et al (2010) found it predicted decreased vermis activity in an adult sample. The opposite brain effects in adult vs. child samples mirror those found in the genetic association literature, where meta-analysis supports an association of the 10R allele with ADHD in childhood (Faraone et al., 2005; Yang et al., 2007), and the 9R allele with ADHD in adulthood (Franke et al., 2010).

Working memory, task-related suppression of DMN, and alterations in DAT protein levels, have all been proposed independently as endophenotypes for ADHD. These proposals are supported by the following evidence: (1) Deficits in WM performance are related with a

large effect size to ADHD in childhood (Willcutt et al., 2005) and adulthood (Hervey et al., 2004), and alterations in neural circuitry supporting WM have been found in adults and children ADHD (Vance et al., 2007; Wolf et al., 2009; Bayerl et al., 2010; Valera et al., 2010); (2) Adult subjects with ADHD show alterations in DMN connectivity (Castellanos et al., 2008; Uddin et al., 2008), and in childhood ADHD subjects show reduced task-related suppression of DMN (Fassbender et al., 2009; Peterson et al., 2009); (3) Meta-analyses have supported an association between alleles in *DAT1* 3'-UTR VNTR and ADHD (Yang et al., 2007; Gizer et al., 2009; Franke et al., 2010), molecular imaging studies have shown altered levels of DAT availability in ADHD subjects (see Krause, 2008 for review), and administration of methylphenidate works at least partially by blocking DAT (Volkow et al., 1998). As reviewed above, all three of these systems are interrelated, however, their relationship to each other has not been studied together in ADHD.

We tested the effect of *DAT1* 3'-UTR VNTR variation on both task-positive and task-negative networks associated with WM, and how these networks relate to ADHD in adulthood. To this end, we evaluated genotype effects in task-positive and task-negative regions of interest (ROIs) in a group of adult ADHD and control participants while they performed an N-back WM task. To understand the relationship of these brain response patterns to ADHD, we tested diagnosis effects in the ROIs, and the relationship of activity and suppression during our N-back task to ADHD symptoms. Based on the literature reviewed above, we hypothesized that adult ADHD would be associated with the 9R allele, decreased activation in task positive regions, and decreased task-related suppression of DMN. Further, given the established link between decreased task-related suppression and inattention to task, we hypothesized that task-related suppression in DMN would be negatively related to DSM-defined symptoms of inattention.

2. Methods

This study is a secondary data analysis, integrating neuroimaging data collected in one study (MH062152) which lasted from 2001–2008, and genetic data collected in MH062152, or in one of four other studies (MH57934, HD37694, MH064019, HD36317). Previous imaging reports have been published on subsets of this sample (Valera et al., 2005; Seidman et al., 2006; Makris et al., 2007; Biederman et al., 2008; Monuteaux et al., 2008; Brown et al., 2010; Valera et al., 2010), but none examining the effect of a gene variant on brain activity during the N-back task. All studies were conducted in accordance with the Declaration of Helsinki and the standards established by the Partners Healthcare Human Research IRB. Written informed consent was obtained from all participants. Participants include all individuals for whom both the N-back fMRI task and DNA were collected, and who met the inclusion criteria for this analysis.

2.1. Participants

Participants were recruited from Massachusetts General Hospital (MGH) clinics and advertisements posted in the Boston area. Exclusion criteria were an estimated full scale IQ <80; lifetime history of psychosis; recent alcohol or substance dependence or abuse; inadequate command of the English language; sensorimotor handicaps. Additional inclusion criteria were age 18–53, self-identified as Caucasian, and carriage of two common *DAT1* 3'VNTR alleles (9-repeat and/or 10-repeat). The resulting sample included 91 adult participants: 53 with ADHD, and 38 controls. Participants with ADHD were told to withhold taking their psychostimulant medication for at least 24 hours previous to the scan. Of the 53 participants with ADHD, 23 (43.4%) reported taking stimulants near the time of scan but had washed out, 20 participants with ADHD (37.7%) had never taken psychostimulants, and the remaining 9 (17.0%) participants had taken psychostimulants at some point in the past.

2.2. Assessment methods

To assess for psychiatric diagnoses we administered the Structured Clinical Interview for DSM-IV (SCID-I; First et al., 1997). To assess ADHD, we used a module derived from the Schedule of Affective Disorders and Schizophrenia for School-Age Children—Epidemiologic Version (K-SADS-E; Orvaschel & Puig-Antich, 1987). This module systematically acquires information on all DSM-IV ADHD symptoms, domains of impairment and age at onset. Previous work has shown that retrospective childhood diagnoses of ADHD can be made in a reliable and valid manner using this method (Biederman et al., 1990; Faraone et al., 2000). An ADHD diagnosis was made if the DSM-IV criteria were met in childhood and persisted into adulthood. At the time of the clinical interview, the distribution of ADHD subtypes was: combined, $N=17$ (32%); inattentive, $N=18$ (34%); hyperactive/impulsive, $N=1$ (2%); and remitted, $N=17$ (32%). Subjects with remitted ADHD were below the DSM-IV 6-symptom threshold at the time of the interview but met criteria including childhood onset and persistence into adulthood. Block Design and Vocabulary subtests from the Wechsler Adult Intelligence Scale-III (WAIS-3; Wechsler, 1997) were used to estimate IQ. Academic achievement was assessed with Reading and Arithmetic subtests from the Wide-Range Achievement Test (WRAT-3; Jastak & Jastak, 1993).

2.3. Genotyping methods

Genotyping of the *DAT1* 3'-UTR VNTR was conducted at the MGH Psychiatric and Neurodevelopmental Genetics Unit using the same protocol as described in several previous reports from our group (Mick et al., 2006; Brown et al., 2010). Briefly, Genomic DNA (5 ng) was amplified in a 7 ml reaction using HotStarTaq DNA Polymerase (0.2 U), the proprietary HotStarTaq Buffer (1 μ l), dNTPs (200 mM), and the marker specific primers (0.2 mM). Primers were ordered from Applied BioSystems and are as follows: SLC6A3-F 6FAMTGTGGTGTAGGGAACGGCCTGAG, SLC6A3-R CCTCCTGGAGGTCACGGCTCAAGG. The SLC6A3-R primer also contains the proprietary tail. For amplification, samples were heated at 92°C for 9 min to activate the HotStarTaq Polymerase. This is followed by 12 cycles of denaturation for 30 sec at 93°C, annealing for 30 sec beginning at 64.5°C and dropped 0.5°C every cycle, and primer extension at 72°C for 30 sec; 37 cycles of denaturation for 30 sec at 93°C, annealing for 30 sec at 58°C, and primer extension at 72°C for 30 sec; 72°C for 1 hr. Amplified products were pooled and combined with size standard (LIZ-250) before being analyzed on an ABI-3730. GeneMapper v3.5 was used to analyze the raw results from the ABI3730, however, a genotype was not considered final until two technologists had independently checked (and corrected) the GeneMapper results and were in agreement.

2.4. fMRI paradigm

We used a variant of the sequential letter visual “N-back” task as described in previous publications from our group (Valera et al., 2005; Whitfield-Gabrieli et al., 2009; Valera et al., 2010). Briefly, the task contained intermittent blocks of the 2-back working memory condition, the 0-back vigilance condition, and a baseline fixation condition. N-back stimuli were generated using MacStim software running on a Mac iBook G4, and projected onto a screen situated in the rear of the magnet bore. Stimuli were viewed through a mirror attached to the head coil. Responses were collected using an MRI safe button box.

Stimuli were sequences of white capital letters on a black background, presented centrally (200 ms duration, 1800 ms inter-stimulus interval) in pseudo-random order. Participants were instructed to respond to every stimulus using a response box, pressing one button to signal targets and another to signal non-targets. In the 0-back condition, the target was the letter “X” (23% of trials), and all other stimuli were non-targets. In the 2-back condition, the

target was any letter identical to the letter that preceded it two trials back, “2-back” (26% of trials).

Participants were administered three runs of the task, each lasting 5.6 minutes. Each run of trials incorporated a block design with 12 epochs: 1) three 36-second epochs of 0-back; 2) three 36-second epochs of 2-back; and 3) six 20-second epochs of “fixation”. Each of the three runs contained alternating 0-back and 2-back blocks, each preceded by a fixation block. Two condition orders were constructed, one beginning with fixation and then 0-back, one beginning with fixation and then 2-back. Condition order was randomized across runs and subjects. Percent of correct responses (accuracy), mean RT for correct responses (speed), and intra-subject standard deviation (variability) were used as performance measures.

2.5. Demographic and behavioral data analysis

Demographic and behavioral data were analyzed in PASW Statistics 18.0 ©. 2×2 ANOVAs with group (ADHD vs. controls) and genotype (9R-carriers vs. 10R-homozygotes) as fixed factors were run on demographic, clinical, and N-back performance data. We created genotype groups based on carriage of the 9R allele for several reasons. First, our sample only included 8 participants with two 9R alleles -- 7 ADHD, 1 Control -- *Ns* too small for a random effects analysis. Second, this grouping has been the convention for previous imaging genetics studies not just in ADHD (Durston et al., 2005; Durston et al., 2008; Bedard et al., 2010), but also in normal controls (Schott et al., 2006; Dreher et al., 2009). Finally, the 9R allele appears to have a dominant effect on DAT availability (van Dyck et al., 2005; van de Giessen et al., 2009).

2.6. fMRI acquisition and analysis

Imaging data was collected using a Siemens Sonata 1.5T full-body scanner at the MGH/HST Athinoula A. Martinos Center for Biomedical Imaging. fMRI was performed with an echo-planar imaging pulse sequence (21 axial slices, TR=2000ms, 5mm thickness, 1mm interslice interval, TE=40ms, flip angle=90°, 168 volumes/run).

fMRI data were analyzed with Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, London). Preprocessing included correction for head motion, spatial normalization, and spatial smoothing with a Gaussian filter (8-mm full width at half maximum). We dropped any single runs that contained more than 3mm of scan-to-scan head motion, stimulus correlated motion of $r \geq 0.5$, or accuracy of less than 68% on the WM task. This resulted in dropping single runs from 7 controls and 9 participants with ADHD, and 2 runs from 2 ADHD participants. However, because all participants were administered 3 runs, we were able to retain these subjects by including remaining runs in our analysis.

After preprocessing, statistical analysis was performed at the single-subject level. Each epoch of trials was modeled using a boxcar function convolved with a canonical hemodynamic response function. Low-frequency components of the blood-oxygen-level-dependent (BOLD) signal were modeled as confounding covariates. Our contrast of interest was the activation associated with the 2-back condition using the 0-back condition as a control baseline, as in previous studies (Cohen et al., 1994; Valera et al., 2005; Valera et al., 2010). Individual contrast maps were submitted to a second-level analysis in which subjects were treated as random effects.

To test main effects and interactions in our contrast of interest, we ran a 2×2 ANOVA with diagnosis and genotype as fixed factors. A voxel-level threshold of $p < 0.005$ uncorrected with an extent threshold of $K > 5$ voxels was used to define significant clusters within our

two *a priori* ROIs which were used as search areas (see below for ROI definition). Cluster-level *p*-values reported are corrected for the number of voxels across the entire respective ROI.

To test the relationship between ADHD symptoms and brain response, we ran bivariate Pearson correlations between the number of symptoms endorsed on the structured interview with mean signal change during the 2-back condition in each of our four correlation ROIs (see below), in the ADHD subjects only. Given the previously identified relationship between inattention and DMN suppression, we also specifically explored the relationship between number of symptoms endorsed on the inattentive subscale and brain response in the correlation ROIs.

2.7. Regions of interest

Anatomical regions of interest (ROIs) were created from the AAL library (Tzourio-Mazoyer et al., 2002) as found in WFU Pickatlas v 2.4 (Maldjian et al., 2003). The task-positive ROI was constructed to include areas found in meta-analysis to be maximally activated during N-back tasks (Owen et al., 2005). This ROI included a union of the AAL-defined supplementary motor area (SMA), middle cingulum (dACC), cerebellar vermis, lateral superior and middle frontal gyri (DLPFC), inferior parietal lobules, caudate, and putamen. The task-negative ROI was constructed to include mePFC (containing anterior cingulum, frontal medial orbital, frontal superior medial), posterior cingulum, and precuneus (Buckner et al., 2008).

For brain-symptom correlations in the ADHD subjects, we created four independent functionally defined ROIs derived from regions of peak signal change across the 53 ADHD subjects. These ROIs were defined as 5mm spheres surrounding voxels of peak activation and peak suppression in the anterior and posterior brain during the 2-back vs. 0-back contrast. Beta values describing the mean signal change in the 5mm spheres were used for correlations. Voxels of peak suppression identified were in left subgenual anterior cingulate (sACC [-3 36 -9]) and left posterior cingulate (PCC [-3 -18 42]). Voxels of peak activation were identified in R DLPFC [39 36 30] and L Inferior Parietal Lobule [-30 -66 51].

3. Results

3.1. Genotype results

Of the 91 participants, 46 were homozygous for the 10R allele, and 45 were 9R-carriers (8 were 9R/9R, 37 were 9R/10R). This is not an unexpected distribution of alleles for a mixed Caucasian sample (Kang et al., 1999), and there was no evidence that these data were not in Hardy-Weinberg equilibrium ($p = 0.89$). As can be seen in Table 1, 12 of 38 controls (32%), and 33 of 53 ADHD participants (62%) were 9R-carriers. There was a statistically significant difference ($\chi^2 = 8.34$, $p = 0.004$), indicating that the 9R allele was more frequent in the ADHD sample.

3.2. Demographic and clinical variables

No significant differences were found between the four groups on any of the demographic, cognitive or comorbidity variables (see Table 1).

ADHD participants did not differ by genotype on any of the clinical variables measured including age of onset, ADHD symptoms in childhood, or symptoms reported at interview (see Table 2). Twelve 9R-carriers (36.4%) and eleven 10R-homozygotes (55.5%) reported taking psychostimulants near the time of scan, but had washed out for at least 24 hours

before the MRI scan. Fifteen 9R carriers (45.5%) and five 10R homozygotes (25%) had never taken psychostimulants. The remaining participants had taken psychostimulants at some point in the past. Proportions of subjects based on psychostimulant history did not differ between genotype groups (see Table 2).

3.3. N-back behavioral performance

There were no significant differences between the four groups on the N-back measures including accuracy, speed, or variability (see Table 1).

3.4. Main effects of task

As expected, the N-back task showed positive activations in a robust network of cortical, subcortical, and cerebellar areas, as well as deactivation across the DMN. Figure 1 and Table 3 display the significant clusters across the entire sample (N = 91).

3.5 Effects of genotype and diagnosis in task-negative ROI

Searching across the task-negative ROI we found a marginal main effect of genotype in the left mePFC (peak voxel $-12\ 51\ 18$, $k = 82$, cluster-level corrected $p = .055$). Examination of beta values from this cluster shows that this effect was due to more task-related suppression in the 9R-carriers compared to 10R-homozygotes (see Figure 2). No main effects of diagnosis and no interactions were found in the task-negative ROI.

3.6. Effects of genotype and diagnosis in task-positive ROI

Searching across the task-positive ROI we found a main effect of diagnosis in the R DLPFC (peak voxel $[36\ 57\ 6]$, $K = 113$, cluster-level corrected $p = 0.047$). Examination of beta values from this cluster shows that this effect was due to reduced BOLD signal change in the ADHD compared to control participants (see Figure 3 top). We also found a marginal interaction effect in the dACC/pre-supplementary motor area (pre-SMA; peak voxel $[12\ 21\ 51]$, $k = 94$, cluster-level corrected $p = 0.081$; see Figure 3 bottom) indicating that 9R genotype predicted decreased activity in this region in the controls and increased activity in the ADHD group. No main effects of genotype were found in the task-positive ROI.

3.7. Relationship of ADHD symptoms to brain response

We found a marginally significant negative relationship of suppression in sACC ($r = -0.237$, $p = 0.088$) and suppression in PCC ($r = -0.241$, $p = 0.082$) to total number of ADHD symptoms endorsed on the structured interview. Total symptoms endorsed were not related to either of the task-positive correlation ROIs (all p 's > 0.72). Suppression in sACC was significantly related to ($r = -0.318$, $p = 0.020$), and suppression in PCC was marginally related to ($r = -0.260$, $p = 0.060$) number of *inattentive* symptoms within the ADHD group, suggesting that greater default suppression predicted more inattentive symptoms (see Figure 4). We did not find any evidence that either of the task-positive peaks were related to inattentive symptoms (R DLPFC: $r = 0.012$, $p = 0.931$; L Inf Par Lobule: $r = 0.055$, $p = 0.695$).

4. Discussion

Our study of the relationship of *DAT1* genotype and adult ADHD to task-positive and task-negative working memory networks yielded four principal findings: 1) we replicated the association of the 9R allele to adult ADHD, 2) we found that 9R-carriers showed marginally greater task-related suppression in mePFC compared to 10R-homozygotes; 3) we found a marginal genotype \times diagnosis interaction in the dACC/pre-SMA, and 4) suppression in

peak regions of the task-negative network predicted a greater number of ADHD inattentive symptoms.

Our first novel finding was a marginal relationship between *DAT1* genotype and task-related suppression in mePFC (p -corrected = 0.055). These data introduce a novel target for *DAT1* and suggest that gene effects on behavior and diagnosis may be at least partially mediated by DMN. The effect of *DAT1* variation on DMN has not, to our knowledge, been studied before in any population. Our findings are, however, consistent with a recent PET-fMRI study by Tomasi et al (2009). They found that lower striatal DAT binding levels predicted greater DMN suppression in healthy adults, and we found that a genotype shown to result in lower striatal DAT expression (Heinz et al., 2000; Mill et al., 2002; Brookes et al., 2007) also predicted greater suppression of DMN. Together, the two findings suggest that genotypic variance in *DAT1* may affect DMN via striatal DA expression.

Our second novel finding was a relationship of task-related suppression of DMN to inattentive ADHD symptoms in adult patients. Based on previous literature supporting a negative relationship between mind-wandering/task-inappropriate thoughts and DMN suppression, we hypothesized that less suppression would predict more inattentive symptoms, but in fact we found that it predicted fewer. Importantly, this finding need be interpreted in the context of a lack of relationship between inattentive symptomology and performance on the n-back task (all r 's < 0.2, all p 's > 0.16), meaning that patients with a greater number of inattentive symptoms performed equally as well on the task as those ADHD participants with fewer inattentive symptoms. The correlation therefore suggests that the more inattentive ADHD subjects needed a greater magnitude of DMN suppression in order to perform the task as well as those participants with fewer symptoms. These findings extend the relationship of task-related suppression to a clinical inattentive phenotype measured outside the scanner, but suggest that these relationships must be interpreted in the context of task performance.

Additionally, we found that the 9R allele was associated with adult ADHD as well as marginally associated with increased DMN suppression; therefore it is not surprising that DMN suppression would predict ADHD severity in adults. These data converge with data from the child literature, which finds an association of both the 10R allele and decreased DMN suppression with ADHD. Thus, it is possible that DMN suppression is directionally linked to the two common *DAT1* alleles, and that while the 10R childhood ADHD risk allele (Yang et al., 2007; Gizer et al., 2009) may predispose towards a lack of DMN suppression (as seen in neuroimaging studies of ADHD children; (Fassbender et al., 2009; Peterson et al., 2009)), the 9R *adult* ADHD risk allele (Franke et al., 2010) may predispose towards increased task related DMN suppression (as suggested by the current study). This relationship therefore poses task-related suppression of DMN on the path from the *DAT1* risk allele to expression of symptoms in both child and adult ADHD.

In this adult sample, we did not find a diagnosis effect anywhere in our task-negative ROI, contrary to previous reports showing decreased task-related suppression in children with ADHD (Fassbender et al., 2009; Peterson et al., 2009). The lack of findings may be related to the high performance rates of both our groups on the fMRI task. Both ADHD and control groups performed the task well, and to equal levels. It may therefore be that task-related suppression is only altered in ADHD when task demands surpass an attentional or difficulty threshold. For instance, Fassbender et al (2009) found that mePFC was significantly less suppressed in those ADHD children who showed greater RT variability. Since we did not find differences in RT variability between the diagnosis groups, it may be that the task parameters associated with DMN alterations in ADHD were not captured by our task, which

may be a function of age (e.g., task more difficult for children). Future studies should test the effect of varying task demands on DMN response in ADHD.

Contrary to findings by Bertolino et al. (2006; 2008; 2009), who found a main effect of *DATI* in DLPFC during N-back tasks, we did not find a main effect of *DATI* anywhere in our task-positive ROI. This discrepancy may be due to a lack of power in our group of control participants carrying the 9R allele, which only contained 12 subjects, or because of our use of ADHD patients and control subjects as opposed to control subjects only. The marginal genotype \times diagnosis interaction effect did however suggest that genotype effects were in different directions in the ADHD and control samples. In ADHD the dACC/pre-SMA was found to be hypoactive in the 10R/10R group, consistent with a previous study in an overlapping sample (Brown et al., 2010) during a different (interference) task. These findings suggest that in task-positive medial wall regions, *DATI* genotype effects may differ in the context of other ADHD-related risk factors.

Our finding of ADHD “hypofrontality” is consistent with many previous neuroimaging studies in both adults and children with ADHD including our own (Valera et al., 2005; Valera et al., 2010), and with dominant theories about the neuroanatomical underpinnings of the disorder (see Paloyelis et al., 2007 for review). The current sample overlaps with an initial report of brain activity during the n-back task by Valera et al (2005) which includes only 27 (30%) of participants in the current report), and with a subsequent report (Valera et al., 2010) which added additional subjects (includes 64 (70%) of participants in current report). In these studies, R DLPFC was found respectively to be marginally and significantly less active in the adults with ADHD, and thus our DLPFC findings are not new. However, the three overlapping reports strongly support DLPFC alterations in adults with ADHD, particularly in its role supporting working memory.

We replicated the meta-analytic study of Franke et al (2010), finding an association between the 9R allele and ADHD in adults. These findings are contrary to the association of the 10R allele to ADHD in children, which have also been confirmed with meta-analysis (Faraone et al., 2005; Yang et al., 2007; Gizer et al., 2009). As mentioned above, it should be noted however that this discrepancy is consistent with our principal brain findings: in ADHD children DMN suppression (which we found to be linked to *DATI*) has been found to be lower in ADHD (Fassbender et al., 2009; Peterson et al., 2009), whereas in our adult sample DMN suppression was found to be increased with ADHD severity.

Limitations of our study include an unbalanced design, so that although we had a large sample size ($N = 91$), power was reduced by our smallest cell ($N=12$). Further, even though genotypes did not statistically differ in terms of ADHD medication history, the mixed history in our sample may be a confound given the effect of psychostimulants on DAT, and the unknown effect of previous psychopharmacological treatment on brain function. We also included ADHD subjects with varied DSM-IV subtypes and participants who had recently remitted from ADHD. Future studies might replicate results with a medication naïve sample, and test the effect of persistence and/or DSM-IV subtypes on brain data and the link to genes. Because data was collected and analyzed over an extended period (2001–2008), future studies should replicate the findings with newer methods. For instance, our paradigm employed a classic block design which has limitations including the inability to model individual responses, and we chose a univariate analytical approach which does not explore connectivity within or across components as can be done with an Independent Components Analysis. Finally, readers should take caution in interpreting the genotype and interaction effects as both of these findings were only marginally significant after correction for multiple comparisons across the entire respective ROI.

Despite these considerations, we found that the 9R allele was associated with both the diagnosis of ADHD and marginally with increased suppression in DMN in adults, the latter of which was associated with a greater number of inattentive symptoms. These findings therefore suggest that task-related suppression of DMN might act as an intermediate phenotype between *DATI* and ADHD. Further, the differences in direction between our DMN findings in this adult sample and those found previously in children mirror the *DATI* gene effects in adults vs. children with ADHD. While the childhood ADHD profile is associated with 10R-homozygosity and decreased task-related suppression in ADHD, our study in adults suggests associations to both the 9R allele and increased DMN suppression. These findings therefore introduce not only a novel neural target for *DATI*, but provide a basis for future longitudinal studies to investigate differences in gene and brain effects between individuals with and without persistent forms of ADHD.

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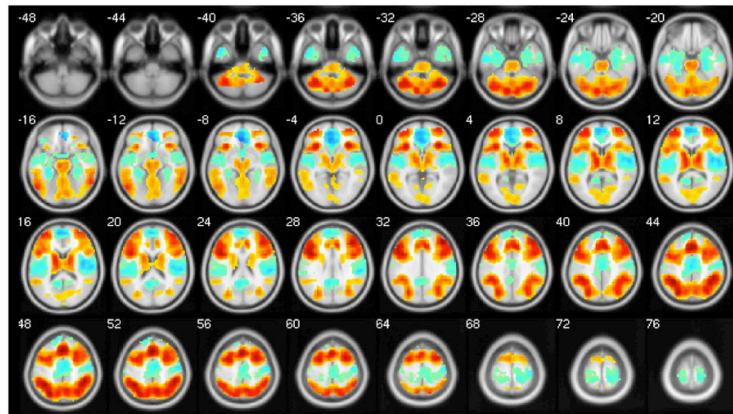


Figure 1.
Main effect of Task (2-Back > 0-Back). Hot colors show areas with positive BOLD signal change, and cool colors show areas with negative BOLD signal change.

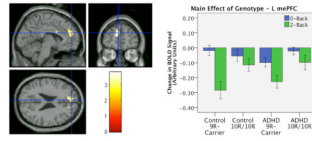


Figure 2. Effects in Task Negative ROI: Trend effect of genotype found in left medial prefrontal cortex (peak voxel $-12\ 51\ 18$, $k = 82$, p -corrected = 0.055). Bars show average signal change across cluster.

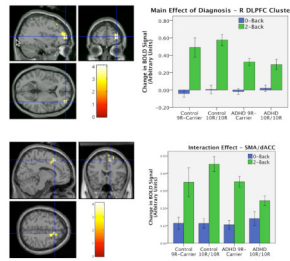


Figure 3.

Effects in task-positive ROI: Main effect of diagnosis (top) found in right DLPFC (peak voxel 36 57 6, $k = 113$, $p\text{-corr} = 0.047$) and trend interaction effect (bottom) in left dACC/pre-SMA (peak voxel 12 21 51, $k = 94$, $p\text{-corr} = 0.081$). Bars show average signal change across cluster.

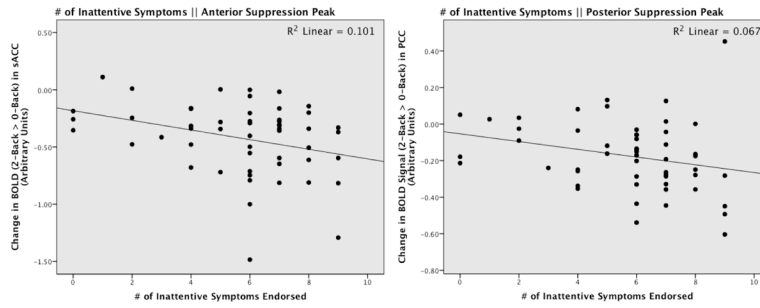


Figure 4. Scatterplots showing relationship of suppression in the sACC (**Left: $r = -0.318$, $p = 0.020$**), and PCC (**Right: $r = -0.260$, $p = 0.060$**) to number of Inattentive Symptoms endorsed at structured interview.

Table 1

Demographic, Cognitive and Performance Data

	Controls						ADHD						Statistic
	9R-carriers (N = 12)		10R/10R (N = 26)		9R-carriers (N = 33)		10R/10R (N = 20)						
<i>Demographic and Achievement Data</i>													
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	
Age	30.7	9.1	31.6	11.2	33.7	10.5	37.6	11.2	37.6	11.2	1.6	0.207	
IQ estimate	119.6	9.2	115.3	11	115.7	14.4	116.9	12.9	116.9	12.9	0.37	0.779	
WRAT Reading	112.9	7.4	107.4	7.6	106.5	9.1	106.4	7.9	106.4	7.9	2.04	0.114	
WRAT Math	105.9	15.6	108.8	10.3	100.7	12.5	101.4	12.3	101.4	12.3	2.4	0.074	
	N	%	N	%	N	%	N	%	N	%	χ^2	p	
Sex (% Females)	6	50	16	61.5	16	48.5	10	50	10	50	1.14	0.777	
% Left Handed	1	8.3	3	13	4	12.1	2	10	2	10	0.16	0.984	
<i>Lifetime Psychiatric Comorbidities</i>													
	N	%	N	%	N	%	N	%	N	%	χ^2	p	
Depression ^a	2	16.7	1	3.8	5	15.2	4	20.0	4	20.0	3.03	0.387	
Anxiety ^b	1	8.3	2	7.7	9	27.3	4	20.0	4	20.0	4.68	0.197	
Dependence ^c	0	0.0	3	11.5	3	9.0	3	15.0	3	15.0	2.01	0.571	
<i>N-Back Performance Data^d</i>													
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	
0 Back - % Correct	97.9	1.7	97.5	5.2	96.9	4.7	97.4	2.2	97.4	2.2	0.19	0.90	
0 Back - RT (ms)	526	67	558	89	556	111	527	73	527	73	0.75	0.52	
0 Back - SD (ms)	129	39	124	32	145	45	135	36	135	36	1.56	0.21	
2 Back - % Correct	88.8	8.7	89.9	6.5	86.9	7.9	87.9	6.7	87.9	6.7	0.85	0.47	
2 Back - RT (ms)	811	140	799	127	815	178	785	157	785	157	0.16	0.92	
2 Back - SD (ms)	248	72	237	53	251	56	245	68	245	68	0.3	0.82	
2 Back - 0 Back RT	284	107	240	86	258	121	258	123	258	123	0.44	0.72	

^a As suggested by others (M. M. Weissman et al., 1984), the diagnosis of major depression was made only if the depressive episode was associated with marked impairment;

^b Since many anxiety disorders are measured by our structured interviews, we aggregated them into a binary measure coded positive if two or more anxiety disorders were endorsed and negative otherwise. We previously found this summary variable to measure a meaningful anxiety syndrome (Mennin et al., 2000);

^cLifetime dependence was found only for alcohol and marijuana;

^dDue to a technical error, n-back performance data was lost for a single ADHD 9R-carrier.

Table 2

Clinical and Medication History in ADHD Subjects

	9R-carriers (N = 33)		10R/10R (N = 20)		Statistic	
	Mean	SD	Mean	SD	t	p
<i>Clinical Data from Structured Interview</i>						
Age of ADHD Onset	4.81	2.49	5.00	2.43	0.27	0.791
Inattentive Sxs – Childhood	7.91	1.18	7.65	1.79	0.58	0.568
Inattentive Sxs – Recent	5.85	2.33	5.45	2.48	0.59	0.559
Hyperactive Sxs – Childhood	6.24	2.32	6.00	2.81	0.34	0.735
Hyperactive Sxs - Recent	4.45	2.82	4.30	2.58	0.20	0.843
<i>Psychostimulant History^a</i>						
	N	%	N	%		
Near time of scan	12	36.4	11	55.0		
Only in past	5	15.2	4	20.0		
Medication Naïve	15	45.5	5	25.0		

^a $\chi^2(2) = 2.52, p = 0.284$; Participants prescribed stimulant medication near time of scan were washed out for at least 24 hours.

Table 3

Main effect of task in whole brain (2-Back > 0-Back; N = 91).

Significant Clusters	Cluster-Level		Voxel-Level (max vox)		
	K (cluster extent)	Corrected p-value	x	y	Z
Task-Positive Cluster					
Pre-SMA; stretching to bilateral Mid & Inf Frontal Gyri, Sup & Inf Parietal Lobule, dACC, Ant & Post Lobe of Cerebellum, Precuneus, Thalamus, Striatum, and Mid Occipital Gyri	35961	p < 0.001	0	21	48
17.64					
Task-Negative Cluster					
sACC; stretching to bilateral Medial Frontal Gyri, Insula, Post Cingulate, Precuneus, Angular/Supramarginal Gyri, Postcentral Gyri, Paracentral Lobule, Sup & Mid Temporal Gyri, and Parahippocampal Gyri	11461	p < 0.001	-3	36	-9
14.27					

Clusters listed are those with p < .05 cluster-level corrected for whole brain. Coordinates are in MNI. Anatomical regions defined using Talairach Daemon atlas, with max vox as first region listed. P-values are cluster-level corrected for whole brain.