Neural and genetic underpinnings of response inhibition in adolescents with attention-deficit/hyperactivity disorder
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Chapter 5

VARIATION IN SEROTONIN NEUROTRANSMISSION GENES AFFECTS NEURAL ACTIVATION DURING RESPONSE INHIBITION IN ADOLESCENTS AND YOUNG ADULTS WITH ADHD AND HEALTHY CONTROLS

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Under review at the Journal of Psychiatry and Neuroscience
Abstract

**Background:** Deficits in response inhibition have been associated with attention-deficit/hyperactivity disorder (ADHD). Given the role of serotonin in ADHD and impulsivity, we postulated that genetic variants within the serotonin pathway might influence response inhibition.

**Methods:** We measured neural activation during stop-signal task performance in adolescents and young adults with ADHD (N=185), their unaffected siblings (N=111), and healthy controls (N=124) (age=16.9), and investigated the relationship of two serotonin polymorphisms (the rs6296 SNP of the *HTR1B* gene and HTTLPR variants of the *5-HTT* gene) with the neural correlates of response inhibition. Additionally, we tested if these variants were associated with the ADHD phenotype and response inhibition performance, and whether they could explain our previously found association of ADHD with neural activation during response inhibition.

**Results:** The whole-brain analyses demonstrated large scale neural activation differences in the inferior and medial frontal and temporal/parietal regions of the response inhibition network between the different variants of both the *HTR1B* and *5HTT* genes. Activation in these regions was significantly associated with stop-task performance, but not with ADHD diagnosis or severity. No associations were found between the *HTR1B* and *5HTT* variants and ADHD or ADHD-related neural activation during response inhibition.

**Conclusions:** These results provide novel evidence that serotonin may play an important role in the neurobiology of response inhibition. Although response inhibition is strongly linked to ADHD, genetic variants associated with response inhibition and its neural correlates do not explain variance of the ADHD phenotype.
Introduction

Serotonin neurotransmission has a link with both cognitive control and impulsivity, one of the defining characteristics of attention-deficit/hyperactivity disorder (ADHD) (see for a review Cools, Roberts, & Robbins, 2008). A main cognitive control function is the process of response inhibition, or the ability to withhold, delay, or alter an already initiated response. Response inhibition is associated with impulsivity (3) and has therefore been extensively studied in relation to ADHD (4; 5). Recently, neural correlates of response inhibition have been reported as potential endophenotypes for ADHD, going beyond purely behavioral measures (6; 7).

On one hand, evidence for the link between serotonin and impulsivity stems from studies of tryptophan (the 5-HT precursor) depletion. Testing the effects of acute tryptophan depletion in healthy human volunteers demonstrated that tryptophan depletion increased impulsive behavior (8; 9), but did not alter stop-signal response inhibition performance (10). However, tryptophan depletion was shown to be associated with decreased neural activation in the response inhibition network even in the absence of altered behavioral response inhibition performance (11). Thus, these results suggest that neural measures may offer more insight into the mechanisms underlying the influence of serotonin neurotransmission on response inhibition.

Also, genetic studies have indicated that impaired serotonergic transmission is associated with increased impulsivity (12). A meta-analysis (13) has indicated two serotonin-related gene variants as risk factors for ADHD. The first is the HTTLPR long allele of the 5-HTT (or SLC6A4) serotonin transporter gene. On the other hand, it is the S allele that has been associated with lower serotonin availability (14). Genetic association studies have also shown inconsistent results for this polymorphism. The S allele of HTTLPR has been linked with heightened impulsivity in healthy participants (15). However, other studies have reported no association between the HTTLPR S allele and impulsivity (16), or even the opposite effect, with increased impulsivity for carriers of the L allele (17).

The second serotonergic genetic polymorphism implicated in ADHD in the meta-analysis of Gizer et al. is the rs6296 single nucleotide polymorphism (SNP) G allele in the HTR1B serotonin receptor gene. This G allele is part of a haplotype block causing decreased HTR1B expression (18), leading to decreased serotonin transmission (19; 20). The rs6296 G allele has been implicated in both trait impulsivity (21) and psychiatric disorders like depression, bipolar disorder, and substance abuse (20; 22; 23), suggesting a role for HTR1B in both cognition and psychiatric disease phenotypes.

Polymorphisms of the serotonin transporter and receptor genes have also been linked to response inhibition performance in healthy participants (i.e., the HT1A C-1019G polymorphism and rs6296, respectively) (Beste, Domschke, Radenz, Falkenstein, & Konrad, 2011; Stoltenberg et al., 2006), and, importantly, have been shown to influence both impulsivity and response inhibition performance in individuals with ADHD (Oades et al.,
So far, studies are lacking on the role of \textit{HTR1B} or \textit{SHTT} in the neural correlates of response inhibition, both in healthy controls and individuals with ADHD.

Given the previously found associations between serotonin genes, impulsivity, and ADHD, the goal of the current study was to investigate the role of \textit{SHTT} and \textit{HTR1B} variants on the neural correlates of response inhibition, behavioral performance, and the clinically defined ADHD phenotype in a sample of adolescents with ADHD, their unaffected siblings, and healthy controls. Inclusion of unaffected siblings enabled us to examine the role of familiality in the distribution of genetic risk factors as well as neural activation patterns. Particularly, we aimed to assess the role of the HTTLPR and rs4696 polymorphisms in this sample using three methods: First, we investigated whole-brain neural activation during response inhibition in relation to these polymorphisms. Second, we investigated if the HTTLPR and rs4696 polymorphisms were associated with ADHD diagnosis and response inhibition performance. Last, we tested if these variants could explain the differences in neural activation in regions that exhibit differential brain responses in ADHD. We expected that the rs6296 and HTTLPR variants associated with higher impulsivity might also influence response inhibition, reflected in decreased activation in the response inhibition network, which in turn might explain variance in the ADHD phenotype.

\textbf{Methods}

\textbf{Participants}

Participants were part of the NeuroIMAGE study, the Dutch follow up of the International Multicenter ADHD Genetics (IMAGE) study. Details concerning informed consent, recruitment, demographics, diagnostics, and testing procedures can be found in the NeuroIMAGE methods publication (24). Within the current sample, we included participants with ADHD (N=184), their unaffected siblings (N=111), and healthy controls (N=124). Participant demographics for our study are listed in Table 1.

\textbf{Stop Signal Task}

Response inhibition was measured using a version of the Stop-Signal task (25) adapted for functional magnetic resonance imaging (fMRI) (26). Participants were instructed to respond as quickly as possible to a go-signal, unless the go-signal was followed after a short interval by a stop-signal (25\% of trials), in which case they were instructed to withhold their response. By varying the delay between go- and stop-signal, it was possible to derive the main outcome measure of the task, the Stop-Signal Reaction Time (SSRT), which reflects the time necessary for a participant to successfully inhibit their response in 50\% of the stop-trials. Secondary outcome measures were the number of omission and commission errors on go-trials (errors) and the Intra-individual component of variation (ICV), derived by
Serotonin transporter variants affect neural activation during response inhibition in adolescents with ADHD and healthy controls

Serotonin transporter variants affect neural activation during response inhibition in adolescents with ADHD and healthy controls

5

dividing the reaction time variability by the mean reaction time over all go-trials. The task consisted of a total of four blocks of 60 trials, separated by one minute intervals.

Task outcome analyses were performed in SPSS (version 19.0, SPSS Inc.), General Estimated Equations (GEE) regression models were used to correct for familial relations between siblings. Separate regression models were executed for SSRT, ICV errors, and MRT, with age, gender, and IQ added as covariates. A significance threshold of 0.05 was entrained for all analyses.

Genotyping

An extensive description of DNA extraction and genotyping of the HTTLPR VNTR in IMAGE is provided elsewhere (27). The rs6296 SNP was genotyped using KASPar analysis at the Radboud university medical center, details can be found in the Supplementary Information (SI).

fMRI acquisition and analysis

FMRI data were collected at two sites using similar Siemens Scanners and identical coils and protocols, and were processed using FSL FEAT (FMRIB’s Software Library, www.fmrib.ox.ac.
uk/fsl; version 6.0). Details regarding acquisition, preprocessing and first-level analysis can be found in the SI.

**Genetic effects on ADHD diagnosis and task performance**

The diagnostic group factor consisted of three groups of interest, i.e., participants with ADHD, unaffected siblings, and unrelated controls. The effects of diagnosis and behavioral response inhibition were investigated using chi-squared statistics and analysis of variance respectively (see Tables 2 and 3).

**Role of genetic variants on whole-brain activation in the combined ADHD-control sample**

To investigate the effect of each genetic variant on task activation at the whole brain level, two separate higher-level analyses were conducted. An F-contrast was constructed for each polymorphism, treating the three possible rs6296 genotypes or the three HTTLPR genotypes as primary between-participant factor. ADHD diagnosis was entered as a second factor in order to investigate possible mediation or interaction effects. Age, IQ, gender, and scan site were added as nuisance regressors in all group-level analyses. Statistical inference was done after initial thresholding at a voxel-level (Z < 2.3) using Gaussian random field (GRF) theory-based cluster statistics at $p < .05$ (FSL cluster; (28)). Post-hoc tests using GEE models in SPSS were performed for beta values from clusters showing significant main effects of genetic variants to specify the direction of the genetic effects and to investigate potential effects of diagnostic group.

Additional models were run to associate the extracted beta-values with stop-task performance as well as with the number of ADHD symptoms. Besides the abovementioned covariates, family membership was added as a between-participant factor in all abovementioned models to account for the family structure of our data.

**Sensitivity analyses**

Sensitivity analyses were performed using similar GEE models to investigate any potential confounding effects of age, gender, IQ, and scanner-site on whole-brain activation, together with tests investigating the potential effects of stimulant medication use and duration (as measured by self-report questionnaire and pharmacist prescription data), as well as the potential effects of comorbid oppositional defiant disorder and conduct disorder.

**Genetic effects on diagnosis-sensitive task responses**

To investigate genetic effects on regions that exhibit differential brain responses in ADHD, we applied region of interest (ROI) analyses. For all three contrasts, ROIs were defined functionally by calculating an F-contrast for the diagnostic group*task effects on neural activation across all participants (see SI, or (7)). Beta-values from these ROIs were exported from the individual contrast maps and subsequently used to test the effect of the three
possible HTTLPR or rs6296 variants. We used GEE models for each ROI separately with the same predictors as mentioned above. Likewise, familial relatedness was entered as a random factor to correct for non-independence of the data. Gender, age, IQ, and scan-site were added as covariates. P-values were corrected for multiple comparisons using Bonferroni-Holm correction (29).

**Results**

**Genetic effects on diagnostic status and task outcome measures**

The distribution of the risk variants did not differ significantly between participants with ADHD, their unaffected siblings, and healthy controls (see Table 2). No significant relations between any of the risk variants and task outcome measures were observed, nor were there any main effects of (or interactions with) age, gender, or IQ (see Table 3).

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Risk genotype</th>
<th>MAF HWE</th>
<th>ADHD no risk</th>
<th>Siblings no risk</th>
<th>Control no risk</th>
<th>Odds Ratio a</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HTT</td>
<td>HTTLPR</td>
<td>LL</td>
<td>.37</td>
<td>.78</td>
<td>65</td>
<td>94</td>
<td>43</td>
<td>58</td>
</tr>
<tr>
<td>HTR1B</td>
<td>rs6296</td>
<td>CC</td>
<td>.26</td>
<td>.29</td>
<td>67</td>
<td>90</td>
<td>44</td>
<td>54</td>
</tr>
</tbody>
</table>

Note: MAF = minor allele frequency; HWE = Hardy-Weinberg equilibrium
a Odds Ratio illustrate the relative distribution of genotypes between participants with ADHD and healthy controls.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Polymorphism</th>
<th>Risk genotype</th>
<th>SSRT a</th>
<th>ICV a</th>
<th>Errors a</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HTT</td>
<td>HTTLPR</td>
<td>LL</td>
<td>.751</td>
<td>.687</td>
<td>.685</td>
</tr>
<tr>
<td>HTR1B</td>
<td>rs6296</td>
<td>CC</td>
<td>1.016</td>
<td>1.696</td>
<td>.428</td>
</tr>
</tbody>
</table>

Note: SSRT = Stop-signal reaction time; ICV = Intra-individual coefficient of variance; Errors = Number of omission and commission errors on go-trials. Bold values indicate significant outcomes.

a Gene effects on the stop-task outcome measures were derived from generalized estimating equation model corrected for familiality, age, gender and IQ.

**Genetic effects on whole-brain fMRI activation**

Both HTTLPR and rs6296 genotype significantly influenced the neural activation in the successful stop–go and failed stop – go contrasts. We found differential activation for the HTTLPR genotypes in the left frontal pole, right cerebellum, and right inferior/orbitofrontal
gyrus during successful stop trials. During failed stop trials, nodes of differential activation were found in the right inferior frontal gyrus, frontal pole, cingulate gyrus, and the brainstem (See Figure 1). Post-hoc tests indicated that in every case the effects were driven by altered neural activation in the SS genotype as compared to the SL and LL genotype; with the SS genotype showing decreased activation in the frontal nodes and increased activation in posterior nodes as compared to the other two genotypes (see Table 4).
Rs6296 genotype was associated with differential activation in anterior cingulate, occipital, inferior temporal, and cerebellar regions during successful stop trials. During failed stops, inferior and superior frontal gyrus, superior parietal gyrus, occipital cortex, and precuneus were differentially active (see Figure 2). Post-hoc tests indicated that these group effects were mainly driven by the difference between the CC genotype and CG and/or GG genotype. However, the direction of these effects was inconsistent, with both increased and decreased activation for the CC genotype being observed in frontal and posterior nodes (see Table 4).
### Table 4. Role of HTTLPR genotypes in brain activation during the Stop Signal Task

#### Effects of HTTLPR on neural activation

<table>
<thead>
<tr>
<th>Successful-stop contrast</th>
<th>Side</th>
<th>#Voxels</th>
<th>P</th>
<th>F</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>frontal pole</td>
<td>L</td>
<td>113</td>
<td>&lt;.001</td>
<td>2.89</td>
<td>-36</td>
<td>62</td>
<td>16</td>
<td>SS &lt; SL = LL</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>89</td>
<td>&lt;.01</td>
<td>3.71</td>
<td>48</td>
<td>-54</td>
<td>-40</td>
<td>SS &gt; SL = LL</td>
</tr>
<tr>
<td>inferior/orbitofrontal gyrus</td>
<td>R</td>
<td>90</td>
<td>&lt;.01</td>
<td>3.95</td>
<td>46</td>
<td>20</td>
<td>-14</td>
<td>SS &lt; SL = LL</td>
</tr>
</tbody>
</table>

#### Failed-stop contrast

<table>
<thead>
<tr>
<th>Side</th>
<th>#Voxels</th>
<th>P</th>
<th>F</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>inferior frontal gyrus</td>
<td>R</td>
<td>195</td>
<td>&lt;.0001</td>
<td>3.81</td>
<td>48</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>frontal pole</td>
<td>R</td>
<td>140</td>
<td>&lt;.001</td>
<td>3.29</td>
<td>42</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>cingulate gyrus</td>
<td>R</td>
<td>113</td>
<td>&lt;.01</td>
<td>3.69</td>
<td>6</td>
<td>-46</td>
<td>-2</td>
</tr>
</tbody>
</table>

#### Brainstem

<table>
<thead>
<tr>
<th>Side</th>
<th>#Voxels</th>
<th>P</th>
<th>F</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/R</td>
<td>113</td>
<td>&lt;.01</td>
<td>4.09</td>
<td>-2</td>
<td>-32</td>
<td>-20</td>
<td>SS &gt; SL = LL</td>
</tr>
</tbody>
</table>

#### Effects of rs6296 on neural activation

<table>
<thead>
<tr>
<th>Successful-stop contrast</th>
<th>Side</th>
<th>Volumes</th>
<th>P</th>
<th>F</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum</td>
<td>L</td>
<td>246</td>
<td>&lt;.0001</td>
<td>3.52</td>
<td>-32</td>
<td>-48</td>
<td>-28</td>
<td>CC &gt; GC = GG</td>
</tr>
<tr>
<td>lateral occipital cortex</td>
<td>L</td>
<td>190</td>
<td>&lt;.0001</td>
<td>3.4</td>
<td>-42</td>
<td>-90</td>
<td>-4</td>
<td>CC &gt; GC</td>
</tr>
<tr>
<td>anterior cingulate gyrus</td>
<td>R</td>
<td>183</td>
<td>&lt;.0001</td>
<td>3.73</td>
<td>16</td>
<td>42</td>
<td>8</td>
<td>CC &lt; GC = GG</td>
</tr>
<tr>
<td>cerebellum</td>
<td>R</td>
<td>146</td>
<td>&lt;.0001</td>
<td>3.61</td>
<td>26</td>
<td>-38</td>
<td>-50</td>
<td>CC &gt; GC = GG</td>
</tr>
<tr>
<td>lateral occipital cortex</td>
<td>L</td>
<td>121</td>
<td>&lt;.001</td>
<td>3.31</td>
<td>-42</td>
<td>-72</td>
<td>-16</td>
<td>CC &lt; GC</td>
</tr>
<tr>
<td>inferior temporal gyrus</td>
<td>L/R</td>
<td>90</td>
<td>&lt;.05</td>
<td>3.09</td>
<td>-48</td>
<td>-70</td>
<td>26</td>
<td>CC &lt; GC</td>
</tr>
</tbody>
</table>

#### Failed-stop contrast

<table>
<thead>
<tr>
<th>Side</th>
<th>Volumes</th>
<th>P</th>
<th>F</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>precuneus</td>
<td>L/R</td>
<td>348</td>
<td>&lt;.0001</td>
<td>3.7</td>
<td>-2</td>
<td>-62</td>
<td>16</td>
</tr>
<tr>
<td>lateral occipital cortex</td>
<td>R</td>
<td>223</td>
<td>&lt;.0001</td>
<td>3.45</td>
<td>54</td>
<td>-68</td>
<td>32</td>
</tr>
<tr>
<td>superior frontal gyrus</td>
<td>L</td>
<td>162</td>
<td>&lt;.0001</td>
<td>3.39</td>
<td>-6</td>
<td>54</td>
<td>28</td>
</tr>
<tr>
<td>superior parietal lobe</td>
<td>L</td>
<td>131</td>
<td>&lt;.001</td>
<td>3.93</td>
<td>-24</td>
<td>-54</td>
<td>48</td>
</tr>
<tr>
<td>inferior frontal gyrus</td>
<td>R</td>
<td>116</td>
<td>&lt;.01</td>
<td>2.98</td>
<td>60</td>
<td>20</td>
<td>32</td>
</tr>
</tbody>
</table>

---

**Role of genetic effects in whole-brain fMRI activation, stop-task performance, and ADHD severity**

During successful response inhibition, the right inferior/orbitofrontal area that was differentially activated for the different HTTLPR genotypes was also associated with SSRTs (B=-.113, $\chi^2=9.511$, p=.002), indicating better response inhibition with increased activation in this node. Both the right inferior/orbitofrontal area and left frontal pole were additionally associated with error rates (B=0.921, $\chi^2=6.986$, p=.008; B=0.95, $\chi^2=9.217$, p=.002, respectively), both indicating increased error rates with higher neural activation in these clusters (see SI).
Neural activation in the right anterior cingulate gyrus that showed differential activation for the HTR1B genotypes was negatively correlated with SSRT ($B=-.061$, $\chi^2=9.083$, $p=.003$) during successful inhibitions, indicating increased inhibition performance with higher anterior cingulate activation. No other significant correlations between neural activation and task performance survived correction for multiple comparisons (see SI).

No significant associations were found between the activation in neural nodes indicated in the whole-brain analysis and either ADHD diagnosis (ADHD, unaffected sibling, or control), nor the number of ADHD symptoms, indicating no relation between ADHD status and the effects of rs6296 and HTTLPR on neural activation.

**Influence of covariates on whole-brain fMRI activation**

To investigate whether the whole-brain activation was influenced by age, gender, IQ, scan site, medication use, and comorbid disorders, several post-hoc analyses were performed. No main or interaction effects of IQ, gender, or scan-site were detected, indicating that these variables did not influence the reported genetic effects on fMRI activation. The activation in the right inferior frontal and frontal pole areas where differential effects of the HTTLPR genotypes were observed during failed inhibitions also showed a main effect of age ($B=-1.197$, $p=.011$; $B=2.637$, $p=.005$, respectively), indicating a general decrease of activation in these nodes with increased age. However, there was no interaction with the gene effect in the same location, indicating that both effects occur independently. No other effects of age were observed.

The effects of medication were assessed by incorporating both medication use and duration of use in post-hoc analyses, as were the effects of comorbid diagnoses of oppositional defiant disorder and conduct disorder. None of the medication and comorbidity factors showed main effects or interaction with the genetic effects on the reported neural activation.

**Genetic effects on differential fMRI activation between diagnostic groups**

The main diagnostic group contrast on neural activation during the stop-task indicated differential activation between participants with ADHD, unaffected siblings, and controls in a range of nodes in inferior and superior frontal, anterior cingulate, and temporal/parietal areas. Details regarding these ROIs can be found in (7) as well as in the SI. None of the multivariate tests indicated main (neither with nor without incorporation of the diagnostic effect) or interaction effects with group of rs6296 or HTTLPR genotypes on the neural activation in these ROIs (see SI).
Discussion

In the present study, we investigated the effects of two genetic variants, HTTLPR in the serotonin transporter gene and rs6296 in the serotonin receptor gene HTR1B on response inhibition performance and its underlying neural activation patterns in a cohort consisting of participants with and without ADHD. We provide for the first time direct evidence for a genetically driven effect of serotonin transmission on the neural correlates of response inhibition.

The first part of this study was to test the effects of two genetic variants within 5HTT and HTR1B on whole-brain activation during response inhibition. These analyses indicated effects of HTTLPR in the frontal nodes of the response inhibition network, as well as in more posterior nodes like the cerebellum and cingulate cortex. Specifically, decreased neural activation was observed in individuals with the SS genotype in the right inferior frontal gyrus and frontal poles; the former is recognized as an essential node of the response inhibition network (30; 31). On the other hand, increased neural activation in individuals with the SS genotype was observed in the cerebellum, cingulate cortex, and brainstem. Lower activation in the right inferior frontal region was associated with decreased response inhibition performance during successful stop-trials, although lower activation in the same region as well as in the frontal pole were also associated with lower error rates on go-trials, suggesting a possible deficit in response inhibition, but an increase in general attention performance on go-trials in individuals with the SS genotype (32).

Our results indicate that the effect of HTTLPR on neural activation is driven by the SS genotype, which showed less activity in the frontal response inhibition nodes and more in the posterior areas. The relations between neural activation and stop-task performance further indicate that these frontal areas are directly involved in response inhibition and attentional performance; although no direct effect of HTTLPR genotype on performance was observed. Taken together, these findings might indicate a posterior shift of neural activation in individuals with the SS genotype, possibly compensating for decreased activation of the main response inhibition network. Given decreased serotonin availability in individuals with the SS genotype (14), these findings may signal a relation between lower serotonin availability, decreased response inhibition, and increased impulsivity (15). However, this would be in conflict with the meta-analytic findings marking the L carriers of the HTTLPR as an ADHD risk-group, given that decreased neural activation in frontal nodes during response inhibition has usually been associated with ADHD severity, including in the current sample (7), although a study also reported an association between the S allele of the HTTLPR and adults with ADHD (33). Another study compared different types of impulsivity paradigms in rats, demonstrating that tryptophan depletion may influence reactivity on go-trials, but not stop-signal reaction times in a go/no-go task. This indicates that while the delay discounting aspect of impulsivity may have been affected, response inhibition was not (34). These findings may explain our current effects of HTTLPR on neural activation, which showed
opposite effects on neural activation levels, error rates, and SSRTs. This dissociation between different aspects of impulsivity will need to be further investigated to fully understand the relation between serotonin, impulsivity, and ADHD.

The effect of rs6296 showed a similar distribution across frontal-parietal, occipital, and cerebellar nodes, equally indicating relatively widespread differential activation. The GG genotype, considered an ADHD risk factor (13), showed increased activation in occipital, temporal/parietal, superior frontal, and cingulate regions, with decreased activation in cerebellar and inferior frontal areas. Of those, activation in anterior-cingulate regions was significantly associated with SSRT length, indicating higher activation levels correlated with better inhibition performance. Temporal parietal, superior frontal, and cingulate regions have all been implicated in attentional control and action monitoring processes necessary for response inhibition (26; 35; 36). In addition, previous studies have suggested the involvement of a separate frontal-thalamo-cerebellar pathway involved in inhibitory control (37). The current results may suggest decreased activation in the frontal-cerebellar pathway in G allele carriers, compensated by increased activation in attentional of top-down control areas. We postulate that the utilization of compensatory or alternative strategies using attention resources may explain the lack of direct effects of rs6296 on stop-task performance.

In the second part of the study, we investigated whether variants in the 5HTT and \textit{HTR1B} genes were associated with ADHD diagnosis, response inhibition, or whether previous outcomes detailing the influence of ADHD on neural activation during response inhibition were related to variants in the 5HTT and HTR1B genes. We found that the HTTLPR and rs6296 variants were not associated with ADHD diagnosis, nor did they influence the ADHD effect on behavioral or neural measures of response inhibition. These findings therefore suggest there is no direct causal pathway between the genetic variants investigated, response inhibition, and the ADHD phenotype. There may be several explanations for these results. First, the main limitation of the current study is that we tested only a small part of the functional variants in the serotonin system. Recent studies have suggested that the cumulative variance across a large number of genes within a single pathway may offer additional explanatory power over the single gene variant approaches (38). Future research should consider a broader scope of functional gene variants across neurotransmitter systems that may be required to fully establish or dissociate the genetic links between response inhibition and ADHD. Second, response inhibition and the variants HTTLPR and rs6296 from the 5-HTT and HTR1B genes have been implicated in a wide range of psychiatric disorders including depression, bipolar disorder, anxiety, and substance abuse disorder (22; 39; 40). This may indicate possible shared genetic and neural underpinnings of different psychiatric disorders. The abovementioned findings suggest that diagnostic boundaries between psychiatric disorders may not necessarily represent underlying genetic mechanisms (41); and the current findings suggest that the use of neurobiological constructs may provide more specific targets for genetic studies than diagnostic phenotypes.
To summarize, whole-brain analysis of neural activation indicated a broad pattern of differential neural activation in frontal-parietal, cerebellar, and occipital areas during response inhibition associated with HTTLPR and rs6296. Activation in these nodes was related to response inhibition performance, but independent of ADHD diagnosis and severity. These results demonstrate the effect of the HTTLPR and rs6296 variants on the behavioral and neural correlates of response inhibition. Since there were no direct associations between the genetic variants and task performance, neural correlates may be a more sensitive measure of genotype effects than solely behavioral or clinically defined phenotypes.
References


Serotonin transporter variants affect neural activation during response inhibition in adolescents with ADHD and healthy controls


Chapter 6

DISCUSSION
In the current section I will summarize the main findings and added value of the research in this thesis, and further interpret these findings within the relevant literature and theoretical frameworks. Additionally, I will shortly investigate the clinical applications and future directions of the current research lines.

**Main conclusions regarding the neural correlates of response inhibition**

The main findings regarding the biological underpinnings of response inhibition from the first two research chapters of this thesis include:

- Neural activation during both successful and failed inhibition contrasts was localized in inferior and medial frontal, basal ganglia, temporal/parietal and cerebellar nodes.
- The third contrast, failed-successful inhibition, showed activation in anterior cingulate and inferior frontal nodes.
- Neural connectivity measures indicate a network of positive connectivity including inferior frontal, superior frontal, putamen and temporal/parietal areas during successful inhibition.
- Neural connectivity measures indicate a network of negative connectivity including medial prefrontal, precuneus, temporal and cerebellar nodes during successful but not failed response inhibition.

The results in the first two chapters of this thesis were based on a large and well characterized sample of adolescents and young adults with ADHD that is unique in its size and age-range. Another asset is that both activation and connectivity measures were analyzed in the same data-set. This allowed us to both replicate and expand upon much of the existing studies on response inhibition. Taken together, we can draw several conclusions regarding the nature of response inhibition based on the findings in these two chapters.

First, in chapter 1, we demonstrated that the neural correlates of the response inhibition processed are distributed across a large network of nodes, including not only the classical areas in the inferior frontal gyrus, pre-supplementary motor area and basal ganglia, but also cingulate, temporal-parietal, precuneal areas and cerebellum.

Both cingulate (1; 2) and temporal-parietal activation (3–5) have previously been associated with response inhibition in the literature, and have been indicated to play a role in action/error monitoring and attentional allocation respectively. We reliably observe activation in these regions over all subjects during response inhibition, and activation in these nodes is associated with performance measures such as error rates and reaction time variability measures. These findings indicate the importance of recognizing that other cognitive processes are continuously involved in stop-task performance, largely independent from the response inhibition process itself. Specifically when using the stop-
task to investigate differences in response inhibition between groups, we should keep in mind that other cognitive processes are at work which may influence our measurements, yet are also interesting measurement targets of their own. In the current thesis we have tried to optimally separate these processes in our analyses and interpretations, but further research will be necessary to accurately distinguish all sub-processes contributing during stop-task performance. Specifically, paradigms measuring response inhibition whilst manipulating attentional demands load would be specifically useful in this regard.

Second, the cerebellum and precuneus have received limited attention within the response inhibition and ADHD literature to this point, even though the cerebellum has recently been indicated as a prime node in the frontal-striatal-cerebellar network which underlies response inhibition performance (6–8), and differences in cerebellar volumes have been found in several studies (9; 10). Future studies should be aimed at delineating the causal role of the cerebellum in response inhibition within ADHD, and investigate whether differences in connectivity with cerebellum are associated with either volumetric changes and/or altered neural correlates of response inhibition in ADHD.

Furthermore, the connectivity analyses over all subjects from chapter 3 demonstrated the added value of connectivity measures when investigating the neurobiology of response inhibition. Those results indicated that apart from the positive connectivity between nodes of both frontal-striatal and a frontal-parietal network, a large amount of negative connectivity was also found, specifically during successful inhibitions. This is in contrast with the neural activation maps, where only positive activation as compared to the baseline go-trials was found (see Figure 1).

![Figure 1: Task activation during the successful stop – go contrast over all subjects, for the Neural Activation (A) and PPI (B) analyses.](image)

Indeed, several interesting observations can be made when comparing the differences in PPI connectivity between participants with ADHD, unaffected siblings and controls with the activation differences reported in the first chapter. The connectivity and activation data have similar effect sizes, as the average Cohen’s d is 0.425 for connectivity betas and 0.407 for
activation clusters. And since the PPI analysis is corrected for the main task-contrast, the resulting correlation between PPI and task activation betas was very low ($r=-0.02$, $SD=0.04$). This indicates that both the connectivity and activation betas uniquely explain variance in the ADHD phenotype. These observations further support the added value of employing both activation and connectivity analyses within fMRI research.

Our connectivity results suggested that the suppression of task-irrelevant nodes or networks, specifically the default mode network, is also essential to proper response inhibition performance. Our results also indicate that by looking purely at the activation levels during an fMRI task, we are missing a large part of the neural correlates of the response inhibition process. The relative scarcity of functional connectivity studies of response inhibition in the general population makes further interpretation of these results in our own sample difficult. Future research should definitely take connectivity measures into account when investigating the neurobiology of inhibitory control.

Finally, we demonstrated relatively similar patterns of activation during both successful and failed inhibition. The failed – successful stop contrasts indicated differences in activation levels in inferior frontal and cingulate regions, indicating increased activation in the response inhibition and error monitoring networks during or following failed inhibitions. This is also conform the previous literature (11; 12), and the presence of these nodes in both separate contrasts further indicates that there is no qualitative difference in neural activation between successful and failed stop trials, but merely a quantitative one.

**Main conclusions regarding the role of response inhibition in ADHD**

The main findings regarding the differences in the neural correlates of response inhibition between subjects with ADHD, their unaffected siblings and healthy controls from the first two research chapters of this thesis include:

- Participants with ADHD, compared to healthy controls, show longer stop-signal reaction times, as well as higher error rates and higher reaction time variance during response inhibition performance. Unaffected siblings of the participants with ADHD do not differ from healthy controls in any of these measures.
- Participants with ADHD, compared to healthy controls, show decreased neural activation during both successful and failed inhibitions in inferior, superior and medial frontal nodes, as well as supramarginal and cerebellar areas.
- Participants with ADHD show lower connectivity between left inferior and superior frontal seed regions and right inferior frontal, striatal and supramarginal regions as compared to healthy controls.
- Proband with ADHD show higher connectivity with medial prefrontal, temporal and cerebellar regions.
Both activation and connectivity measures from the main nodes of the response inhibition network are correlated with ADHD severity, and correlated with behavioral stop-task performance.

Unaffected siblings show largely intermediate patterns of activation and connectivity, in between probands with ADHD and healthy controls. However, they also show uniquely lower connectivity between inferior frontal seed regions and the primary motor areas during successful inhibition, compared to healthy controls.

These results provide several novel insights regarding the network of neural nodes affected in ADHD, and the way these nodes are integrated, as well as the link with task-performance and ADHD severity. The inclusion of unaffected siblings in this design further allowed us to draw conclusion about the familial nature of the abovementioned effects. Taken together, we can draw the following conclusions from these data:

First, we demonstrated that the alterations in neural activation in adolescents with ADHD are not restricted to the narrow definition of the frontal-striatal response inhibition network as often used in the response inhibition literature on healthy subjects (i.e. (13)). Instead, we showed alterations in a large range of nodes including temporal-parietal, dorsolateral-prefrontal, cingulate and cerebellar nodes. These nodes are associated with different functional networks, involved in attentional, monitoring and top-down control related processes (3; 5; 14; 15). These findings, specifically since they are associated with altered behavioral indices, like reaction time variance and/or error rates, suggest that there are other cognitive processes involved in altered stop-task performance in ADHD besides response inhibition. Specifically, general attentional deficits have been linked with increased performance variance in probands with ADHD within a variety of paradigms (16; 17). Increased variability in mean reaction time, as well as errors on the go-trials, will influence the algorithmic estimation of the eventual stop-signal reaction time. Therefore, general attentional deficits will indirectly influence response inhibition performance. In the current thesis, we incorporated measures of error rates and reaction time variance in all statistical models to maximally separate the effects of the attentional processes and response inhibition proper. Further, we used the correlation between behavioral task outcome measures and fMRI activation/connectivity patterns to maximally dissociate the influence of these cognitive processes on the task-outcome and eventual behavior. Nonetheless, specialized paradigms might be required to specifically measure the interaction between attention related processes and response inhibition. For example, the stop-task variant introduced by (18) allowed the separation of proactive and reactive inhibition, and this design is currently being adapted to incorporate different levels of working memory demands. Similarly, an attempt could be made to vary attentional demands during this task, by incorporating distracters or other irrelevant stimuli. This would allow us to further dissociate attentional processes from proactive and reactive response inhibition processes.
Second, the relation between neural measures and both task-performance and ADHD symptom severity indicated that we can use neural measures to explain a part of the behavioral phenotype. Altered neural activation and connectivity are related to both task performance and ADHD severity across all subjects. However, given the relatively small effect sizes for these correlations over the entire group, and the relatively large within-group variance in neural measures, these results may indicate that the coupling between neural activation profiles, neuropsychological performance and phenotypic outcome measures may differ between subgroups within the sample. It may therefore be informative to investigate whether subgroups based on neurocognitive profiles can be defined within the current large sample of participants with ADHD, as is also discussed under the ‘future directions’ section of this thesis.

Uncovering the distinctions between probands with ADHD and their unaffected siblings was another prime example of the utility of neural activation and connectivity measures provided by the current data. We observed no differences from healthy controls in inhibition performance as measured by the SSRT in the unaffected siblings of adolescents with ADHD. However, in both neural activation and connectivity measures signals in frontal-striatal and frontal-parietal nodes of unaffected siblings were intermediate, in between those of probands and healthy controls. These group differences were invisible when looking purely at behavioural inhibition measures; neural measures may thereby help to better define these phenotypic groups, and shed light on the causal influence of the neural alterations found in affected versus unaffected ADHD family members. Additionally, unaffected siblings showed compensatory strategies in the neural connectivity but not activation levels. These results provide evidence for the familial and possibly hereditary nature of the response inhibition deficits, and provide insight into some of the neurobiological mechanisms that underlie the difference between probands with ADHD and their unaffected siblings.

**Main conclusions regarding the role of dopaminergic and serotonergic influence on response inhibition in ADHD.**

- *COMT* and *DAT1* variants influence neural activation levels in lateral and medial prefrontal and supramarginal areas as well as the thalamus during response inhibition.
- *5HTT* and *HTR1B* variants influence neural activation levels in medial and superior frontal, temporal/parietal and occipital areas during response inhibition.
- *COMT* and *DAT1* variants are not associated with ADHD diagnosis, nor do they explain the altered neural activation patterns observed in probands with ADHD as compared with healthy controls.
- *HTR1B* and *5HTT* variants are equally not associated with ADHD diagnosis, and do not explain the altered neural activation patterns observed in probands with ADHD as compared to healthy controls.
The neural activation values in nodes affected by $COMT/DAT1$ and $HTR1B/5HTT$ variance were associated with response inhibition performance.

Results from chapters three and four replicated and expanded upon the literature regarding $DAT1$ and $COMT$ influences on neural activation during response inhibition, and offered new insight into the role of $HTR1B$ and $5HTT$ on the neural correlates of response inhibition within our ADHD enriched sample. The extensive results from the whole-brain analyses, together with the absence of direct associations between the genetic variants and ADHD diagnosis or severity, allowed us to draw several conclusions regarding the genetic background of response inhibition.

First, we demonstrated that both genes from the dopamine and serotonin pathways play a significant role in the neural correlates underlying response inhibition. More specifically, we demonstrated that different $DAT1$, $COMT$, $HTR1B$ and $5HTT$ genotypes showed activation changes in a wide range of neural nodes from both the frontal-striatal and frontal-parietal network, as well as several nodes outside of the established response inhibition networks. Furthermore, these alterations were associated with different response inhibition performance differences. The widely distributed nature of genetic effects, the differences between specific variants including different regions and directions of effects, as well as various different associations between neural activation measures and stop-task outcome measures in chapters three and four all indicated that there is no simple and unitary influence of the dopamine and serotonin pathways on response inhibition. Rather, the monoamine neurotransmitter systems and their genes factors likely together and in an interactive way are involved in response inhibition at the behavioural and neural level. This decreases the chances to find a simple one-to-one mapping from genetic variants to neurobiology to behavioral phenotype.

In sum, our results indicate that the incorporation of neural measures allows us to observe the differential influence of single genetic risk variants on response inhibition, but also suggested that a selection of single risk genes unlikely explain the causal pathways between genotype and behavioral response inhibition performance.

Second, we found no significant associations or interactions between any of our genetic risk variants and ADHD diagnostic status or severity, nor could the variance in these risk genes help explain the aforementioned effects of ADHD on neural activation presented in chapter one. These results further illustrate the difficulties in illuminating direct causal pathways between genes to behavior. Given the relatively small proportion of variance in the behavioral performance explained by variance in our genotypes, and given that the disease phenotype is conceptually an even more complex, higher order concept than response inhibition performance, any significant associations between these genetic variants and the ADHD phenotype may have been too small to observe.

We should take caution in future research to overly interpret effects of single gene variants, particularly so in studies employing relatively small sample sizes. Instead,
we should acknowledge a more cumulative or kaleidoscopic view of genetic influence on behavioral and disease phenotypes, even within the same genetic pathway. The utilization of neural measures will enable a more detailed view of potential interacting or possibly even counteracting genetic influences that may be invisible on one-dimensional measures like task outcome or disease severity.

Lastly, recent studies have suggested limited specificity of both response inhibition as a biomarker for ADHD as well as the specificity of the genetic risk variants used in the current study. In fact, response inhibition deficits have been observed in a range of major psychiatric disorders, like schizophrenia (19) and bipolar disorder (20). Additionally, several large scale genetic studies have showed shared genetic contributions in relation to all these major psychiatric disorders (21). These findings suggest that specific genes do not relate on a one-to-one basis with the diagnostic criteria attributed to a specific disorder (70). Taken together with the results of the current thesis, this research suggests that the use of generic neurobiological endophenotypes may therefore provide more valuable targets for genetic studies than single disease phenotypes.

**Use of Endophenotypes in ADHD research**

Based on the aforementioned associations and lack of associations, what can we conclude about the use of the endophenotype model in ADHD research?

Within the first two chapters of this thesis, we have shown that the use of solely behavioral response inhibition performance measures do not allow the same detailed insight into the distinct processes that are involved in stop-task performance than the brain measures.

The relations between genetic variance and the neurobiology of response inhibition, in the absence of a direct link between genes and ADHD phenotype, further suggests the added value of neurocognitive levels of description when investigating putative links between genetics and behavior. The use of a neurocognitive endophenotype may allow the detection of both small as well as indirect genetic influences otherwise invisible in solely behavioral outcome measures. However, the lack of direct causal relations found between genetic variants and ADHD diagnosis or severity in the current thesis also indicates the limitations of the classical endophenotype model (22). For we found an association between genetic variants and the endophenotype, as well as a relation between this endophenotype and a disease phenotype, without finding a direct mediation between genetic influences, response inhibition and ADHD. However, it should be noted we only looked at several promising genetic variants, and did not consider the larger variation within a single gene, nor polygenic or entire genetic pathway models. Nor were factors like gene*gene or gene*environment interactions taken into account within the current studies. Taken together, these results suggest a potential utility in the addition of neural correlates
to risk gene studies, though more research is needed to fully and definitively explore these effects.

**Clinical implications of the current research**

The research in this thesis was performed primarily to gain insight into the neurobiological nature of response inhibition alterations in ADHD, and additionally to investigate the validity of previous models developed to interpret the causal relations underlying part of the neurobiology of ADHD. The contribution of the results in this thesis consists of both novel insights, leading to deeper understanding and more specific future research goals; but also of negative findings, providing warnings against invalid claims and oversimplified interpretations of the ADHD etiology.

We have demonstrated that neural correlates of response inhibition provide insight into the neurobiological alterations associated with an increased familial risk for ADHD, but we have also found that these alterations are not universal in adolescents with ADHD and their siblings. We reported that the influence of genetic pathways on a phenotype can be illuminated using neural correlates as target measures, but we have also shown the absence of a clear causal pathway between investigated genetic variants and ADHD phenotype.

Therefore, although this thesis has not contributed directly to any clinical diagnostic tool or intervention, it has indicated both the limitations and possibilities of large-scale fMRI based research in ADHD, and has thereby contributed to the unraveling of the ADHD phenotype. The clinical implication of this research may be described as advancing our understanding of ADHD as a disorder, which should eventually lead to more effective risk assessment, diagnostics and treatment.

**Future directions**

In the previous sections we have discussed the novelty of the results presented in this thesis, and how they fit into the existing theoretical frameworks around ADHD and response inhibition. In this section we will extrapolate the current findings, and explore potential future research directions suggested by the current research.

**Neurocognitive subgroups in ADHD**

First, there is the possibility to tackle heterogeneity in the ADHD phenotype by studying subgroups based on neurocognitive measures. Nearly all behavioral and neural outcome measures investigated in the current thesis showed a wide range of within-group variance, indicating significant heterogeneity within the probands with ADHD. A recent line of research has suggested that this may be due to the existence of underlying subgroups with
distinct cognitive profiles in probands with ADHD and/or healthy controls (23). Variance in nature and distribution of the cognitive profiles within a disease population like ADHD may account for the variability of deficits on different (neuro) cognitive measures as well as weak or absent (i.e., too small to detect) genetic effects.

In order to investigate the validity of neurocognitive subgroups, and integrate this knowledge with the methods used in the current research, we will require detailed insight into the factors determining or accurately describing cognitive profiles. The application of algorithm based, data-driven subgrouping approaches may allow us to investigate these subgroups in an unbiased an hypothesis free manner (e.g. (23–26)). Based on the current thesis, we may be able to draw some preliminary conclusions on the applicability of these approaches. First of which is that the incorporation of multiple measurements from different neural, cognitive and behavioral methodologies may aid in the endeavor to more closely describe the ADHD phenotype, and discover potential subgroups therein. The utility of algorithm based subgrouping approaches will depend on the comprehensiveness of our datasets, with data from distinct modalities and different levels of description providing the best opportunity to estimate the shared variance between subgroups. Specifically, machine learning approaches have been suggested to offer a potentially more objective and reliable way to distinguish diagnostic subgroups, utilizing combinations of both cognitive and neural measures to identify the pattern of features which together best differentiate between the diagnostic groups and subtypes (e.g. (27–29)).

Furthermore, increasing the number of factors taken into account when studying the relations between genetics, neurobiology, cognition and phenotype may additionally enable the study of more complex genetic causal pathways; incorporating cumulative gene variance or entire pathway variance as well as gene*gene or genes*environment interactions. Additionally, there may potentially be causal pathways between genes and behavior that are only valid within certain neurocognitive subgroups within our population (30).

**Sample sizes in genetic-fMRI research**

The large sample size of the NeuroIMAGE study allowed us to make robust and generalizable inferences regarding the neural correlates of response inhibition in ADHD; however, our relatively large sample size did not result in replication of previous associations described associations between ADHD the candidate genes studied in chapters three and four. These results may indicate that individual candidate genes have only small effects on the ADHD phenotype, and earlier results in small samples may have overestimated these effects.

The cumulative amount of explained genetic variance within ADHD is still very low (31). Specifically, genome-wide association studies (GWAS) have had very limited success in discovering new genetic variants associated with ADHD outside of the hypothesis based risk variants. Even though GWAS consortia have collected and pooled data from thousands of subjects with and without ADHD, significant results remain scarce and the explained
variance of the genetic background for ADHD remains low (32). One of the developments in this field is the further collaboration between different consortia, further increasing the numbers of subjects in the hope of raising enough statistical power to counteract the massive multiple comparisons problem involved with the simultaneous and hypothesis-free testing of hundreds-of-thousands of common genetic variants. Within chapters three and four we demonstrate another potential line of development, utilizing hypothesis based selection of genetic variants, in combination with biologically defined outcome measures as endophenotypes. We demonstrate that when using only single genetic variants in combination with fMRI based outcome measures can help unraveling the causal relations between genes and cognition. By expanding these methods to incorporate multiple genetic variants, for example multiple variants with a single gene, or a-priori selection of specific genetic pathways (33) it is possible to increase the explanatory power, and observe in more detail the interactions between genetic factors and environment, while still avoiding the massive multiple comparisons problems endemic in GWAS based studies.

Developmental changes and longitudinal scans

Another topic of future interest is the development of neural and cognitive profiles within ADHD over time. Within the current thesis, using a cross-sectional design, we consistently find that both behavioral performance and neural measures normalize with age. This effect is consistent with the observation of larger cognitive deficits during the first measurement within this sample during the IMAGE research (34), when our sample had a mean age of twelve as compared to seventeen years during the current measurements.

Due to the significant changes in brain development over adolescence (35), it will be very relevant to observe how the neural correlates of response inhibition develop with age, and if the validity of neural measures as an endophenotype for ADHD remain in adulthood. Additionally, longitudinal measurement of response inhibition performance will allow for investigation of the predictive value of fMRI measures during adolescence; i.e. we will be able to track disease development and persistence in adulthood, and test if these developments can be predicted using the neural correlates of response inhibition in the current sample (e.g. (36; 37)).

The longitudinal nature of the NeuroIMAGE project will allow us to pursue these topics in future research, and establish better descriptive and predictive models of remittance and persistence in ADHD over development.
References:


