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Response inhibition in Parkinson's disease and impulsive-compulsive spectrum disorders

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Abstract

Over the past 20 years, motor response inhibition and interference control have received considerable scientific effort and attention, due to their important role in behavior and the development of neuropsychiatric disorders. Results of neuroimaging studies indicate that motor response inhibition and interference control are dependent on cortical–striatal–thalamic–cortical (CSTC) circuits. Structural and functional abnormalities within the CSTC circuits have been reported for Parkinson's disease and many neuropsychiatric disorders, including impulse control disorders, obsessive–compulsive disorder (OCD) and related disorders, such as attention-deficit hyperactivity disorder, Tourette's syndrome, and trichotillomania. Parkinson's disease and the neuropsychiatric disorders also share impairments in motor response inhibition and interference control, which may underlie some of their behavioral and cognitive symptoms. Results of task-related neuroimaging studies on inhibitory functions in these disorders show that impaired task performance is related to altered recruitment of the CSTC circuits. Previous research has shown that inhibitory performance is dependent upon dopamine, noradrenalin, and serotonin signaling, neurotransmitters that have been implicated in the pathophysiology of these disorders. In this narrative review, we discuss the common and disorder-specific pathophysiological mechanisms of inhibition-related dysfunction of disorders within the impulsive-compulsive spectrum.

Introduction

Response inhibition, the ability to suppress pre-potent behavior that is inappropriate or no longer required, is critical for goal-directed behavior in everyday life (Chambers *et al.* 2009). Over the past decades, researchers have shown increased interest in response inhibition. Response inhibition is considered an operationalization of certain aspects impulsivity and compulsivity (Bari and Robbins 2013a). Impulsivity is commonly defined as a tendency to act on impulses, acts performed immediately and without voluntary control, whereas compulsivity is the tendency to repeat specific behavior and to be unable to inhibit the behavior even when it is no longer appropriate (Bari and Robbins 2013a). Due to the importance of response inhibition in everyday life, many neuropsychological paradigms have been developed to probe inhibitory performance. In these paradigms, subjects are asked to respond to a target stimulus, but withhold this response to irrelevant or distracting stimuli, or distracting stimulus characteristics (Nigg 2000).

Response inhibition is not a unitary construct and consists of motor response inhibition and interference control. Motor response inhibition involves the inhibition of pre-potent and automatic motor responses, and can be further differentiated into action restraint (or action suppression) and action cancellation (Schachar *et al.* 2007). The Go/No-go task (Donders 1969/1868) is considered to probe action restraint, whereas the Stop signal task (Logan 1994) measures action cancellation (see figure 7.1 for a description of these tasks). Interference control on the other hand, refers to the cognitive control needed to prevent interference due to competition of relevant and irrelevant stimuli or stimulus characteristics (Nigg 2000). Several tasks including the Stroop task, the Flanker task and the Simon task are measures of interference control (see figure 7.1). It has been proposed that the inhibitory load is highest in the Stop signal task, as the response that needs to be suppressed has already been initiated (Schachar *et al.* 2007). Contrary to the motor response inhibition tasks, interference control tasks may also rely on response selection processes (Nee *et al.* 2007). It has been suggested that interference control, action restraint and action cancellation represent early, intermediate and late processes of response inhibition, respectively (Sebastian *et al.* 2013a).

The symptoms of disorders within the impulsive-compulsive spectrum, such as impulse control disorders, obsessive-compulsive disorder and attention-deficit hyperactivity disorder are characterized by a failure to inhibit certain behaviors, e.g. washing hands, pulling hair, motor tics, gambling, or impulsive actions (but see Potenza *et al.* 2009). Response inhibition might therefore be a suitable measure to investigate the neural substrates of these shared symptoms. In this narrative review, we will provide an overview of studies that have examined the neuroanatomical and functional underpinnings of response

inhibition impairment in healthy subjects and patients with these disorders. In addition, we will use Parkinson's disease (PD) as a model for cortico-striatal dysfunction and its relation with failures in response inhibition; and describe how such dysfunction may lead to the development of impulse control disorders in a subgroup of PD patients. This review focuses on the shared mechanisms that may underlie the inhibitory dysfunction and symptoms of impulsive-compulsive spectrum disorders. Pharmacological and genetic alterations are also addressed and focus on the dopamine, serotonin and noradrenalin system. We acknowledge that other neurotransmitters, such as glutamate and gamma-Aminobutyric acid, are also important for response inhibition and the pathophysiology disorders within the impulsive-compulsive spectrum (MacMaster *et al.* 2003; Turner *et al.* 2003; van Minnen *et al.* 2003; DeVito *et al.* 2005; Starck *et al.* 2008; Silveri *et al.* 2013), but discussion of all these neurotransmitters would considerably lengthen this review.

Neural correlates of response inhibition in healthy controls

Neuroimaging of response inhibition

Neuroimaging studies in healthy controls have revealed the neural substrates of response inhibition (for excellent reviews see Robbins 2007; Chambers *et al.* 2009; Aron 2011). While major contributions to our understanding of response inhibition come from electrophysiological studies, in this review we will focus on neuroimaging studies. Readers interested in the electrophysiology of response inhibition are directed to (Huster *et al.* 2013).

In brief, response inhibition activates a network of mainly right lateralized frontal brain areas. The inferior frontal gyrus (IFG) and pre-supplementary motor area (pre-SMA) are key components (Aron *et al.* 2003b; Chambers *et al.* 2006; Floden and Stuss 2006; Cai *et al.* 2012), and the neural stop signal is then believed to be sent from these frontal areas to the motor cortex through cortico-striatal-thalamic-cortical (CSTC) projections (Chambers *et al.* 2009).

The subcomponents of response inhibition are found to depend on overlapping, yet distinct, brain areas. Interference inhibition, action restraint and action cancellation are all associated with activation of the IFG, anterior insula, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (DLPFC), pre-SMA and parietal regions (Wager *et al.* 2005; Nee *et al.* 2007; Sebastian *et al.* 2013b). When inhibitory task load increases, activation of frontal-striatal regions increases and additional inhibition-related brain areas are recruited (Blasi *et al.* 2006; Swick *et al.* 2011; Sebastian *et al.* 2013b). However, each task recruits distinct brain areas as well, depending on the unique cognitive processes that they represent. Regions involved in response selection, including the parietal cortex, for instance, are activated to a greater extent during interference control tasks and action restraint (Rubia *et al.* 2001; Sebastian *et al.* 2013b).

Neurotransmitters in response inhibition

In addition to differences in neural activation, differences in the neurotransmitter systems underlying interference control, action restraint and action cancellation have also been observed. Current studies suggest that interference control is dependent on serotonin and dopamine neurotransmission. Depletion of serotonin and dopamine has been shown to decrease interference effects on incongruent trials, and thus improve performance, during the Stroop task (Schmitt *et al.* 2000; Scholes *et al.* 2007). Decreases in serotonin may improve performance by increasing arousal and attention (Scholes *et al.* 2007). Increased activation of the DLPFC and ACC was observed during performance of a Stroop task after serotonin depletion (Horacek *et al.* 2005). Stroop performance was positively correlated with serotonin transporter (SERT) binding in the right DLPFC as well (Madsen *et al.* 2011). However, contradicting results have also been reported, as neuroimaging studies showed that decreased dopamine transporter (DaT) binding in the striatum in women (Mozley *et al.* 2001) and decreased postsynaptic striatal D2 receptor availability was associated with poor performance on a Stroop task (Volkow *et al.* 1998). Administration of a dopamine D2 agonist decreased interference, and thereby improved performance on the Stroop task (Roesch-Ely *et al.* 2005). Based on the available literature in healthy subjects it seems that both serotonin and dopamine are important for interference control.

Action restraint (Go/No-go task) seems to be primarily mediated by serotonin (for a review of evidence see Eagle *et al.* 2008). Serotonin depletion has been shown to decrease activation of the IFG during inhibition and decreases activation of the medial prefrontal lobe during error monitoring in the Go/No-go task (Rubia *et al.* 2005a; Evers *et al.* 2006). Administration of a serotonin 2c receptor agonist (Anderson *et al.* 2002) or mirtazapine (Vollm *et al.* 2006), which acts on both the noradrenalin and serotonin system, increased inhibition-related activation of the right IFG. Nevertheless, dopamine may play a role in action restraint as well since methylphenidate, a dopamine re-uptake inhibitor, improved performance on the Go/no Go task and led to decreased task-related striatal activation (Vaidya *et al.* 1998).

Several lines of evidence support an important role for dopamine in action cancellation. Increased Dopamine D2/3-receptor availability in the striatum is associated with better Stop signal task performance, i.e. shorter stop-signal reaction time (SSRT), and correlates positively with inhibition-related activation of the dorsal caudate and putamen (Ghahremani *et al.* 2012). Also, administration of a D2-receptor agonist improved action cancellation (Nandam *et al.* 2013). Administration of methylphenidate and atomoxetine, which both target the dopamine and noradrenalin system by inhibiting the re-uptake from the synaptic cleft, decreased SSRT in humans and in animals, raising the possibility that noradrenalin is involved in motor response inhibition as well (Chamberlain *et al.* 2006b; Eagle *et al.* 2007; Bari *et al.* 2009; Nandam *et al.* 2011). Serotonin does

not seem to mediate performance of the Stop signal task, as use of selective serotonin reuptake inhibitors (SSRIs) and serotonin depletion did not affect action cancellation in humans or in animals (Clark *et al.* 2005; Chamberlain *et al.* 2006b; Bari *et al.* 2009; Eagle *et al.* 2009; Drueke *et al.* 2010).

To summarize, interference control seems to be mediated by both serotonin and dopamine. Action restraint seems to be predominantly mediated by serotonin, whereas action cancellation seems to be mediated by dopamine and noradrenalin. More detailed information on the neuropharmacology of response inhibition is provided by (Dalley and Roiser 2012; Bari and Robbins 2013a).

Genes in response inhibition

Several gene-association studies have examined the relationship between genes involved in the dopaminergic and serotonergic systems and response inhibition. Genetic polymorphisms in the dopamine D4 receptor gene (DRD4), associated with reduced functional activity (Asghari *et al.* 1995), have been related to decreased performance on the Stop signal task (Congdon *et al.* 2008), although conflicting results have also been reported (Kramer *et al.* 2009).

The DRD2 gene codes for the dopamine receptor D2. The presence of a TaqIA allele, which has been linked to decreased availability of striatal D2-receptors (Thompson *et al.* 1997) was associated with poor response inhibition in the Stop signal task (White *et al.* 2008). A second polymorphism, which has been associated with decreased cortical and thalamic D2-receptor availability (Hirvonen *et al.* 2009), was also related to poor action cancellation (Colzato *et al.* 2010).

Genetic polymorphisms that increased expression of the dopamine transporter (DaT) have been associated with impaired performance on an interference control task (Cornish *et al.* 2005) and decreased brain activation in the subthalamic nucleus (STN) and pre-SMA during action cancellation (Congdon *et al.* 2009). Furthermore, two novel single nucleotide polymorphisms in the DaT gene predicted individual SSRT (Cummins *et al.* 2012) and genotype of one of these polymorphisms predicted activation of frontal areas and the caudate nucleus during task performance.

Polymorphisms in catechol-O-methyltransferase (COMT) and monoamine oxidase A (MAO-A) genes, coding for enzymes playing a role in neurotransmitter metabolism, have been associated with normal variations in inhibition-related activity as well. COMT is involved in the degradation of dopamine and noradrenalin and MAO-A is involved in degradation of dopamine, noradrenalin and serotonin. A polymorphism of COMT with decreased function (Chen *et al.* 2004), was associated with increased activation of the IFG during action cancellation (Congdon *et al.* 2009) and decreased interference inhibition (Solis-Ortiz *et al.* 2010), although conflicting results have also been reported (Kramer *et al.* 2007). Polymorphisms of the MAO-A gene that increase MAO-A activity, were associated with increased activity in the right IFG and ACC and decreased activity

in the superior parietal cortex during action restraint (Passamonti *et al.* 2006).

Gene association studies have focused on genes involved in serotonergic transmission as well. Serotonin synthesis in the brain is regulated by tryptophan-hydroxylase-2 (TPH-2) (Walther and Bader 2003). Individuals homozygous for the T-allele of a polymorphism in the TPH2 gene showed increased SSRT in the Stop signal task (Stoltenberg *et al.* 2006). A second study found that two other polymorphisms in the TPH-2 gene were associated with reduced brain activity during action restraint in an EEG study (Baehne *et al.* 2009). Lastly, Osinsky *et al.* (Osinsky *et al.* 2009) found that a polymorphism located in the promotor region of the TPH-2 gene, affected reaction time during performance of a Stroop task. Interpretation of these findings is, however, challenging as it is uncertain how these polymorphisms affect serotonin levels.

Polymorphisms in the serotonin transporter (SERT) gene (SLC6A4) that decrease the rate of re-uptake from the synaptic cleft, were associated with decreased interference inhibition (Holmes *et al.* 2010), but not to action cancellation (Clark *et al.* 2005). Participants with a decreased function polymorphism in SERT also showed increased rostral ACC activation in response to errors and decreased activation of the dorsal ACC in response to conflict during the Flanker task (Holmes *et al.* 2010).

Intermediate summary

In summary, current evidence suggests that response inhibition is dependent on brain areas in the CSTC circuits and activation in these circuits increases with increasing inhibitory load. Proper function of these CSTC circuits depends on a complex interplay between dopamine, serotonin and noradrenalin, although the weight of their importance may differ between the subcomponents of response inhibition. While reducing levels of serotonin and dopamine appears to ameliorate interference control, increasing dopamine levels appears to ameliorate action restraint and action cancellation. Gene association studies have primarily reported that polymorphisms associated with decreased dopamine signaling are also associated with decreased motor response inhibition performance.

Structural and functional alterations in CSTC circuits and altered serotonin, noradrenalin and dopamine transmission may underlie response inhibition deficits in obsessive-compulsive disorder (OCD) patients and in patients with related disorders.

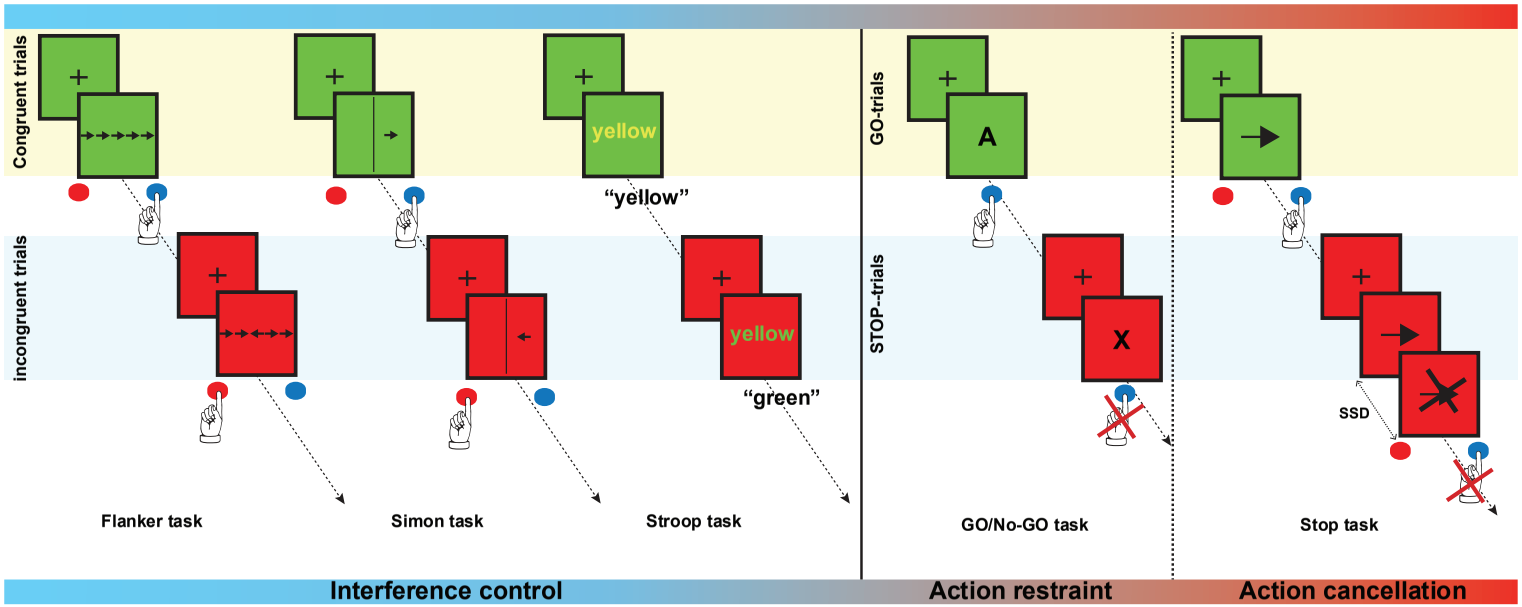


Figure 7.1 – Examples of interference control and motor response inhibition tasks. The Eriksen-Flanker task is a test in which subjects are asked to respond to a target stimulus by pressing a button to indicate the direction of the target stimulus. The target, however, is flanked by non-target and distracting stimuli which are presented in the same or in the opposite direction as the target (congruent and incongruent trials, respectively). During a Simon task, participants are asked to press a button depending on the orientation of the arrow, irrespective of the location of the arrow. Orientation and location can either be congruent of incongruent. In the Stroop task names of colors are presented in either the same (congruent) or a different color (incongruent). Subjects are instructed to name to color of the word but not the word itself. In the Go/no go task subjects need to respond as fast as possible when letters are presented (Go-trials), but must withhold the response when a certain letter (e.g. "X") is presented (Stop-trials). In a Stop signal task the participant is asked to respond as fast as possible by pressing a button to a stimulus (go-trials) that is presented. On a minority of trials a stop signal is presented and the subject is asked to suppress the response when the stop signal occurs. Task demands gradually increase from interference control to action cancellation.

Inhibitory deficits in Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative basal ganglia disorder that leads to depletion of, among others, dopamine, serotonin and noradrenalin (Kish *et al.* 1988; Politis *et al.* 2010a; Goldstein *et al.* 2011). Dopamine is the major neuromodulator in the CSTC circuits and can either facilitate or inhibit their activation depending on the activation of their different receptor subtypes and dopamine concentrations (Alexander *et al.* 1986; Vriend *et al.* 2014c). PD-related dopamine denervation of the CSTC circuits is thought to underlie the typical motor symptoms, but also seems to be involved in some of the non-motor symptoms of the disease (Vriend *et al.* 2014b; Vriend *et al.* 2014d). PD-related dopamine denervation might also lead to inhibitory deficits due to dysfunction of the CSTC circuits. Indeed, multiple studies have shown that PD patients show behavioral impairment in response interference and inhibition compared with healthy controls (Gauggel *et al.* 2004; Wylie *et al.* 2010; Obeso *et al.* 2011a; Filoteo *et al.* 2014; Nombela *et al.* 2014; Ye *et al.* 2014b). See Table 7. 1 for an overview of the reviewed studies. Behavioral performance on interference control tasks seems to be relatively intact in PD patients compared with healthy controls when tasks are simple. Performance decrements start to become evident when task demands increase from response interference to motor response inhibition, for example, when there is a time-constraint on the Stroop task (Filoteo *et al.* 2014), or when the task requires increased attentional resources (Woodward *et al.* 2002).

Neuroimaging studies on response inhibition in PD are relatively scarce. Decreased performance on the Stroop task was associated with decreased volume of the IFG, putamen and entorhinal cortex (Filoteo *et al.* 2014) and ventricular enlargement (Alegret *et al.* 2001), and decreased performance on the Go/No-go task was associated with atrophy of the nucleus accumbens (O'Callaghan *et al.* 2013b). Using fMRI, two Go/No-go studies reported that, compared with healthy controls, PD patients show increased activation of frontal and striatal areas during inhibition (Farid *et al.* 2009; Baglio *et al.* 2011). Furthermore, this compensatory activation was most pronounced during the off-state (Farid *et al.* 2009). Conversely, during inhibition in the stop-signal task both medicated (Ye *et al.* 2014b; Ye *et al.* 2014a) and medication-naïve PD patients (Vriend *et al.* 2015) show decreased activation of the IFG compared with healthy controls. In addition, PD patients versus healthy controls showed decreased functional coupling between the IFG and striatal area (Vriend *et al.* 2014a; Ye *et al.* 2014a). and the finding that ventral striatal dopamine transporter availability correlated positively with inhibition-related activation of the right IFG, suggests that the degeneration of dopamine projections to that area is associated with deficits in impulse control (Vriend *et al.* 2015).

A possible methodological issue of using PD as a model to study response inhibition is that many patients receive dopamine replacement therapy which

makes it difficult to unequivocally determine whether the effects are due to the PD pathology or medication. Nevertheless, studies employing an on/off paradigm showed that levodopa is unable to fully restore deficits in response inhibition (Willemssen *et al.* 2008; Farid *et al.* 2009; Obeso *et al.* 2011b) and medication-naïve PD patients already show functional deficits (Vriend *et al.* 2015). This evidence suggests that the deficits are primarily due to Parkinson pathology. Levodopa did, however, improve performance on the Stroop task, but only in PD patients that scored low on a baseline cognitive flexibility task (Costa *et al.* 2014). Dopamine agonists impaired interference control on a Simon task, but the effect was again dependent on baseline off-agonist performance of the patient. This resembles the inverted U shaped relation between dopamine signaling and interference control (Wylie *et al.* 2012). Other studies that investigated the influence of medication on response inhibition in PD showed that both citalopram (i.e. SSRI) and atomoxetine, a selective noradrenalin reuptake inhibitor (SNRI), are able to enhance inhibition-related activation (Ye *et al.* 2014b; Ye *et al.* 2014a), but only led to behavioural improvements in SSRT in patients at later stages of the disease (Ye *et al.* 2014b). Furthermore, this medication-induced increase in activation was dependent on structural (Ye *et al.* 2014b) and functional integrity (Ye *et al.* 2014a) of the connection between the IFG and striatum.

Due to an interaction between the pathophysiology of PD and dopamine replacement therapy, approximately 15% of all PD patients develop impulse control disorders (ICD) (Weintraub *et al.* 2010a; Vriend *et al.* 2014c). ICD are described as behavioral addictions in which a person no longer has the ability to suppress an impulse, drive or urge that is potentially dangerous to themselves and/or their surroundings (American Psychiatric Association 1994). The prevalence of ICD in the general population lies somewhere between the 1-7 percent (Kessler *et al.* 2006; Kessler *et al.* 2008). See Vriend *et al.* 2014c for an elaborate account on the pathophysiology of ICD in PD. Only a few studies have investigated response inhibition in PD and non-PD patients with ICD. PD patients with ICD, compared with PD patients without ICD, showed a trend-significant decrease in performance on the Go/No-go subtest of the frontal assessment battery (FAB) and made more errors in the interference condition of the Stroop task (Bentivoglio *et al.* 2013). Another study showed that the deficits in Stroop performance were significantly worse in PD patients with hypersexuality compared with PD patients with pathological gambling or no ICD (Vitale *et al.* 2011), although yet another observed no differences on Stroop performance between PD patients with and without pathological gambling (Cera *et al.* 2014). Studies in non-PD patients with pathological gambling have quite consistently shown behavioral deficits in response inhibition compared with healthy controls (Kertzman *et al.* 2008; Roca *et al.* 2008; Odlaug *et al.* 2011; Brevers *et al.* 2012; van Holst *et al.* 2012), although results on studies in patients with internet addiction have been mixed (Sun *et al.* 2009; Dong *et al.* 2012; Ding *et al.* 2014; Ko *et al.* 2014). Furthermore, across studies patients with pathological gambling problems and internet addiction

show hyperactivation activation of the prefrontal cortex, striatum and anterior cingulate cortex during performance of a Go/No-go task (Dong *et al.* 2012; van Holst *et al.* 2012; Ding *et al.* 2014; Ko *et al.* 2014), but hypoactivation of these same brain areas during a Stop task (Li *et al.* 2014). Together these neuroimaging studies show that non-PD patients with ICD are able to – up to a certain point – compensate their performance by increasing their activation of striatal and prefrontal brain areas but performance deficits become evident when task becomes too demanding. To the best of our knowledge no neuroimaging studies have yet been conducted on response inhibition in PD patients with ICD.

In summary, CSTC circuit dysfunction caused by PD is associated with deficits in response inhibition which gives further support to the notion that CSTC projections are important for response inhibition. The response inhibition deficits observed in PD patients also support a role of dopamine, noradrenalin and serotonin, although the beneficial effects of pharmacological treatment are less pronounced for the behavioral than the functional deficits. Furthermore, dopamine replacement therapy may in some PD patients even lead to inhibition failures and clinically significant ICD. Very little research is, however, currently available on the neural correlates of response inhibition in PD patients with ICD and warrants further investigation. A better understanding of how failure of the response inhibition network contributes to the development clinically significant ICD may help in the recognition of at risk PD patients to allow closer monitoring or instigation of preventive treatment.

Obsessive-compulsive disorder and inhibition

OCD is an anxiety disorder that affects 2-3% of the population and causes severe impairment in social and occupational functioning (Ruscio *et al.* 2010). The disorder is characterized by distress- and anxiety provoking obsessions (repetitive intrusive thoughts) and compulsions (repetitive ritualistic behavior), which are performed to diminish anxiety (American Psychiatric Association, 2013). These symptoms are common, as more than 25% of the population experiences sub-clinical obsessions or compulsions in their lives (Ruscio *et al.* 2010). Pharmacotherapy for OCD consists mainly of SSRIs, which suggests involvement of the serotonin system in the pathophysiology of the disorder. Nevertheless, an estimated 40-60% of patients does not respond to this treatment and require additional treatment with atypical antipsychotics, which affects both the serotonergic and dopaminergic system (Denys *et al.* 2004a; Fineberg *et al.* 2005). Neuroimaging studies have strengthened the notion of serotonergic dysfunction in OCD by providing evidence for reduced availability of serotonin transporters in the midbrain, thalamus and brainstem and reduced availability of serotonin 2a receptors in prefrontal, parietal and temporal brain regions (Hesse *et al.* 2005; Perani *et al.* 2008). Abnormalities in the dopamine system have also

been observed in OCD patients, such as increased dopamine transporter levels in the striatum and reduced availability of the D1 and D2 receptors in the striatum (Kim *et al.* 2003; Denys *et al.* 2004b; van der Wee *et al.* 2004; Olver *et al.* 2009).

In the past several years, research interest has focused on response inhibition as a model of OCD symptoms (Chamberlain *et al.* 2005). In support of this, deficits in interference control, e.g. increased reaction times during incongruent trials, have been described in OCD (Bannon *et al.* 2002; Penades *et al.* 2007; Nabeyama *et al.* 2008; Nakao *et al.* 2009; Schlosser *et al.* 2010). A number of studies have used interference control paradigms in OCD research during functional neuroimaging (See Table 7.2; (Fitzgerald *et al.* 2005; Nakao *et al.* 2005a; van den Heuvel *et al.* 2005; Viard *et al.* 2005; Nabeyama *et al.* 2008; Woolley *et al.* 2008; Nakao *et al.* 2009; Page *et al.* 2009; Schlosser *et al.* 2010; Huyser *et al.* 2011; Rubia *et al.* 2011a; Marsh *et al.* 2014). Some studies reported hyperactivation of the ACC in adults and children with OCD following errors and interference control (Fitzgerald *et al.* 2005; Huyser *et al.* 2011), while others reported hypoactivation of the ACC (Nakao *et al.* 2005a; Rubia *et al.* 2011a). Altered inhibition-related brain activation has also been observed in the pre-SMA (Fitzgerald *et al.* 2005; Rubia *et al.* 2011a) and insular cortex (Huyser *et al.* 2011). Increased activation in frontal-striatal regions, including the IFG and putamen, was seen in OCD patients during performance of a Simon task (Marsh *et al.* 2014).

Abnormalities in activation during interference control tasks have also been observed at a network level. Schlosser *et al.* (Schlosser *et al.* 2010) used dynamic causal modeling (DCM) to examine functional connectivity in a fronto-cingulate network during performance on a Stroop task, and found increased connectivity between the DLPFC and ACC in OCD patients compared with healthy controls. Increased functional connectivity between the putamen and the inferior parietal cortex, caudate, thalamus and frontal areas was observed in patients during performance of a Simon task (Marsh *et al.* 2014).

Impaired action cancellation and action restraint has been described for OCD (Chamberlain *et al.* 2007b; Penades *et al.* 2007); patients showed increased SSRT (i.e. slower inhibition) in the Stop signal task and higher error rates on the Go/No-go task compared with healthy control subjects. Deficits in motor response inhibition were also observed in unaffected first-degree relatives of OCD patients (Chamberlain *et al.* 2007b; Menzies *et al.* 2007), suggesting that motor response inhibition may be considered an endophenotype (a trait that is heritable and co-segregates with the illness in families (Gottesman and Gould 2003) of OCD patients.

Structural neural correlates of impaired motor response inhibition in OCD patients have been identified. Deficits in action cancellation in OCD patients and first-degree relatives were associated with increased gray matter volume in the ACC, putamen, caudate, amygdala, parietal areas and the cerebellum, and decreased gray matter volume in the OFC, IFG, ACC, premotor cortex, and regions in the temporal cortex (Menzies *et al.* 2007).

Functional neural correlates of motor response inhibition impairment in OCD have also been identified (see Table 7.3; (Maltby *et al.* 2005; Roth *et al.* 2007; Woolley *et al.* 2008; Page *et al.* 2009; Rubia *et al.* 2010; de Wit *et al.* 2012; Kang *et al.* 2013). Decreased task-related activation is seen in the CSTC circuits during inhibition in OCD patients (Roth *et al.* 2007; Woolley *et al.* 2008; Page *et al.* 2009; Rubia *et al.* 2010; de Wit *et al.* 2012; Kang *et al.* 2013), although, one study reported increased activation of these regions (Maltby *et al.* 2005). In the largest study to date, de Wit *et al.* (2012) found decreased activation of the IFG and inferior parietal cortex during inhibition in unmedicated OCD patients and increased activation of the left pre-SMA. This pre-SMA hyperactivation was present in their unaffected siblings as well. Activation of the pre-SMA correlated negatively with SSRT in patients and siblings, indicating that hyperactivation of the pre-SMA may be considered a compensatory mechanism. Overall, the most consistent finding is decreased activation of the DLPFC, IFG, striatum and thalamus in OCD patients during inhibition (Roth *et al.* 2007; Woolley *et al.* 2008; Page *et al.* 2009; Rubia *et al.* 2010; de Wit *et al.* 2012).

In a recent study we examined functional connectivity during performance of the Stop signal task in unmedicated adult OCD patients, their unaffected siblings and healthy controls (van Velzen *et al.* 2013). We performed psychophysiological interaction (PPI) analyses and DCM and found abnormal connectivity between the IFG and amygdala in patients and their siblings, suggesting that this pattern of connectivity is an endophenotype. Limbic activation may interfere with CSTC circuit activation in OCD. We did not find evidence for altered connectivity between the IFG, pre-SMA and striatum during inhibition. These results warrant replication in other samples.

Two studies have investigated the effects of pharmacological treatment for OCD on response inhibition. Treatment with SSRI's increased task-relevant brain activation during performance of an interference control task along with symptom improvement (Nakao *et al.* 2005b). However, due to the study design it remains unknown if this change in activation occurs secondary to symptom improvement or due to the pharmacological treatment. A second study reported increased activation of multiple cortical and subcortical brain areas during a Go/No-go task in OCD patients treated with SSRIs compared to OCD patients who were not treated with SSRIs (Roth *et al.* 2007). However, this study was crossectional, included small patient groups and did not study the relationship with disease severity.

In summary, OCD patients show impairment in both interference control and motor response inhibition. Prefrontal and other brain areas within the CSTC circuits appear to be hyperactive during interference control, although results have been inconsistent. As task load increases during action restraint and action cancellation, CSTC areas generally become hypoactive compared with controls, although some compensation may occur. Decreased serotonin and increased dopamine transmission in CSTC circuits may underlie the response inhibition

deficits.

The presence of, and functional correlates of response inhibition deficits have also been investigated in disorders related to OCD, such as Tourette's syndrome (TS), trichotillomania (TTM), and attention-deficit hyperactivity disorder (ADHD), enabling the disorder specificity of these cognitive dysfunctions and enabling comparison of these inhibition deficits across these disorders.

Inhibition in other frontal-striatal disorders

Tourette's syndrome

Gilles de la Tourette's syndrome, also known as Tourette's syndrome (TS), is a neurodevelopmental disorder characterized by motor tics and vocal tics (American Psychiatric Association, 2013). TS affects between 0.4 and 1% of the population (Swain *et al.* 2007; Robertson 2008).

Like in OCD, dysfunction of the serotonergic and dopaminergic systems is implicated in the pathophysiology of TS (for a review see Steeves and Fox 2008). Several clinical trials have shown that administration of dopamine antagonists, such as risperidone and haloperidol, are effective in suppressing tics in most patients (Bloch *et al.* 2011; Roessner *et al.* 2011). Neuroimaging studies have reported decreased availability of the D2 and D3-receptors in cortical (OFC, ACC, insula, temporal and occipital cortex) and subcortical areas (thalamus and hippocampus) (Gilbert *et al.* 2006; Steeves *et al.* 2010) and increased striatal DaT availability (Malison *et al.* 1995; Muller-Vahl *et al.* 2000; Cheon *et al.* 2004; Serra-Mestres *et al.* 2004; Liu *et al.* 2010), although conflicting results have also been reported (Singer *et al.* 2002; Hwang *et al.* 2008). Neuroimaging of the serotonergic system in TS has shown increased binding of the serotonin 2A-receptor in many cortical (OFC, ACC, insula, temporal lobe, parietal lobe and occipital lobe) and subcortical areas (thalamus, caudate, hippocampus) (Haugbol *et al.* 2007) and increased serotonin transporter availability in the striatum and midbrain (Wong *et al.* 2008).

There is increasing evidence for frontal-striatal dysfunction in TS (for reviews see Albin and Mink 2006; Felling and Singer 2011). For instance, symptom severity correlated negatively with the degree of activation of CSTC circuits during tic suppression (Peterson *et al.* 1998) and prefrontal cortical thickness (Draganski *et al.* 2010) and volume of prefrontal CSTC areas was decreased in TS patients compared with healthy controls (Draganski *et al.* 2010).

More than 90 percent of all patients with TS also have co-morbid psychiatric disorders, most often OCD or ADHD (Robertson 2011). It has been estimated that between 45 and 60 percent of TS patients suffer from OCD as well (Ghanizadeh and Mosallaei 2009). As in OCD, many studies have investigated whether the involuntary motor symptoms in TS are related to motor response inhibition and interference control. Evidence for this, however, has been mixed; as some

studies report impaired performance (Baron-Cohen *et al.* 1994; Crawford *et al.* 2005; Rankins *et al.* 2006; Channon *et al.* 2009; Eichele *et al.* 2010), especially with increasing task demands, while others do not (Ozonoff *et al.* 1994; Ozonoff and Jensen 1999; Hershey *et al.* 2004; Verte *et al.* 2005; Watkins *et al.* 2005; Channon *et al.* 2006; Ray Li *et al.* 2006; Marsh *et al.* 2007; Raz *et al.* 2009; Sukhodolsky *et al.* 2010). These studies often included TS patients with co-morbid disorders and patients often used psychotropic medication. A meta-analysis of four studies using the Stop signal task in TS found mild inhibitory deficits (Lipszyc and Schachar 2010).

While evidence for behavioral impairment is not straightforward, inhibition-related brain activity seems to be altered in TS (see Table 7. 4). With increasing age, patients with TS, compared with healthy controls, show increased recruitment of CSTC regions during interference control (Raz *et al.* 2009). Greater activation of CSTC areas, which was observed in TS patients during interference inhibition, might be considered a compensatory mechanism (Marsh *et al.* 2007). During motor response inhibition, patients with TS showed increased inhibition-related frontal brain activity in an event-related potential (ERP) study (Johannes *et al.* 2001). The authors noted that compensatory brain activation may explain why studies have not consistently observed response inhibition deficits in TS patients. No difference was found in brain activation between patients and controls during performance of a Go/No-go task, although the sample size was limited (Hershey *et al.* 2004). No study has yet investigated the direct effects of pharmacological treatment on behavioral or functional measures of response inhibition in TS, although see (Wylie *et al.* 2013).

In summary, behavioural inhibitory deficits may be limited to a subgroup of Tourette's patients, as compensatory brain activation during inhibition may conceal behavioral deficits in response inhibition in some patients. Increased dopamine transmission in CSTC circuits may underlie the deficits in response inhibition.

Trichotillomania

Trichotillomania (TTM) is an obsessive-compulsive related disorder (American, Psychiatric Association, 2013). Patients with this disorder experience an urge to pull out their hair, which causes distress and functional impairment. Due to similarities between TTM and OCD, TTM was historically treated with SSRIs. Although initially considered effective in TTM (Stein *et al.* 1997), more recent studies report that SSRIs are ineffective in TTM (Streichenwein and Thornby 1995; van Minnen *et al.* 2003) or only effective in a specific subgroup of TTM patients (Stanley *et al.* 1997a; Gadde *et al.* 2007). More recent clinical trials showed that treatment with atypical antipsychotics, such as olanzapine and aripiprazole, which exert their effects on amongst others, the serotonergic and dopaminergic system, are more promising (Van Ameringen *et al.* 2010; White and Koran 2011).

It has been suggested that TTM symptoms originate from CSTC circuit

dysfunction (Mataix-Cols and van den Heuvel 2006). In support of this hypothesis, structural abnormalities in frontal areas and regions of the striatum have been observed in TTM (Chamberlain *et al.* 2008b). As patients have difficulty suppressing a motor response, i.e. pulling out their hair, deficits in response inhibition may underlie the symptoms of this disorder (Chamberlain *et al.* 2006a).

Research on response inhibition in trichotillomania is limited and conflicting. While performance of a related cognitive control task was unaltered, TTM patients showed deficits in interference control in the Stroop task (Stanley *et al.* 1997b; Bohne *et al.* 2005). Deficits in action cancellation have been reported, and the degree of impairment correlated with disease severity (Chamberlain *et al.* 2006a). Impairment in action restraint was limited to a distinct subgroup of patients with an early onset of the disorder (Bohne *et al.* 2008).

The neural or pharmacological substrates of response inhibition deficits in TTM have not yet been fully elucidated, as no inhibition-related neuroimaging studies have been performed in this patient group. Nor have there been any studies on the effects of pharmacological treatment on response inhibition. TTM patients do, however, exhibit structural abnormalities in CSTC circuit regions associated with inhibition, for instance in the striatum, IFG, SMA and prefrontal areas (Grachev 1997; O'Sullivan *et al.* 1997; Chamberlain *et al.* 2008b), which may underlie response inhibition impairment in TTM.

Attention Deficit Hyperactivity Disorder

Attention Deficit Hyperactivity Disorder (ADHD) is a neuropsychiatric disorder characterized by hyperactivity, inattentiveness and impulsiveness (American Psychiatric Association, 2013). It is a common disorder, as it is thought to affect almost ten percent of school-aged children (Froehlich *et al.* 2007). The neuropharmacology of ADHD is complex and still not well understood. Current evidence suggests that ADHD is characterized by deficits in the noradrenalin and dopamine systems (for a review see Cortese 2012), although some studies show additional involvement of the serotonergic (Oades *et al.* 2002) system. Pharmacotherapeutic treatment of ADHD with methylphenidate, amphetamines or atomoxetine is effective in treating symptoms, presumably through increasing extracellular levels of dopamine and noradrenalin (see Prince 2008 for a review).

Patients with ADHD show behavioral impairments on a number of interference control tasks, including the Simon task and the Flanker task (Rubia *et al.* 2011a; Sebastian *et al.* 2012). Activation of the ACC, IFG, thalamus, SMA, striatum and inferior parietal cortex is decreased in ADHD patients during interference control (see Table 7.5). A recent meta-analysis revealed decreased activation of CSTC areas, including the right IFG, insular cortex, right caudate nucleus, left inferior parietal cortex and left ACC in ADHD patients during performance of the Stroop and the Simon task (Hart *et al.* 2013).

Motor response inhibition is also affected in ADHD. A meta-analysis of 24 Stop-signal paradigm studies showed increased SSRT and mean GO reaction times

in ADHD patients (Alderson *et al.* 2007). Structural abnormalities have been observed in CSTC circuit areas, including the IFG, caudate and globus pallidus (Durston 2003; Sowell *et al.* 2003; Batty *et al.* 2010; Depue *et al.* 2010; Frodl and Skokauskas 2012), leading some to argue that altered brain structure of these areas may underlie the impairments in response inhibition (Chambers *et al.* 2009). Gray matter volume of the right IFG, ACC, caudate nucleus, medial temporal lobe and globus pallidus correlated negatively with task performance in patients (Casey *et al.* 1997; McAlonan *et al.* 2009). Functional neuroimaging studies show reduced inhibition-related activation of the caudate nucleus, IFG and SMA, and increased activation of areas in the temporal and parietal lobe in children and adults with ADHD (see Table 7.6). A recent meta-analysis of twenty-one response inhibition studies revealed hypoactivation of the right ACC, right IFG, right insular cortex, right thalamus, left caudate nucleus and right fusiform gyrus (Hart *et al.* 2013). In addition to decreased frontal-striatal connectivity, altered frontal-parietal connectivity may also play a role in the response inhibition impairment of ADHD (Cubillo *et al.* 2010).

Pharmacological studies show that administration of methylphenidate and atomoxetine improve action cancellation (Aron *et al.* 2003a; Chamberlain *et al.* 2007a; DeVito *et al.* 2009; Coghill *et al.* 2014) and action withholding (Vaidya *et al.* 1998) in ADHD patients, thereby suggesting that deficits in dopamine and noradrenalin underlie motor response inhibition deficits. Furthermore, use of methylphenidate increased prefrontal and striatal activation during performance of a Go/No-go task in ADHD patients (Vaidya *et al.* 1998). Methylphenidate also normalizes activation deficits in prefrontal, parietal, temporal and cerebellar regions during performance of the Stop signal task (Rubia *et al.* 2011b). When effects of atomoxetine and methylphenidate were directly compared, both medications normalized left prefrontal underactivation during performance of the stop signal task, while normalization of the right prefrontal activation was specific to use of methylphenidate (Cubillo *et al.* 2014).

Several candidate gene studies report an association between genotype and response inhibition deficits in ADHD. In patients with ADHD, a polymorphism of the DRD4 gene, which is associated with decreased functional activity of the dopamine D4-receptor (Asghari *et al.* 1995), was related to altered performance on tasks with an inhibitory component (Langley *et al.* 2004; Bellgrove *et al.* 2005), impaired performance on the Stroop task (Loo *et al.* 2008) and reduced prefrontal cortical thickness (Shaw *et al.* 2007).

ADHD patients homozygous for a polymorphism of the dopamine transporter gene associated with increased transporter expression (Brookes *et al.* 2007), showed increased frontal and parietal brain activation during a modulated Go/no-go task (Braet *et al.* 2011), and showed increased activation in the striatum, premotor and parietal cortices during inhibition in the Go/No-go task (Bedard *et al.* 2010). In contrast, a second study found increased striatal activity during inhibition in polymorphisms that result in decreased function (Durston *et al.*

2008).

In individuals with a specific polymorphism of the MAO-A gene, associated with lower levels of MAO-A, ADHD symptoms were related to decreased IFG activation during the Stop signal task (Nymberg *et al.* 2013). MAO-A genotype of ADHD patients was not related to interference inhibition (Liu *et al.* 2011).

In summary, behavioral deficits in interference control and motor response inhibition are prominent in ADHD and associated with decreased volume and hypoactivation of CSTC areas. Results of gene-association studies suggest that reduced inhibitory performance may be related to decreased dopamine transmission in CSTC circuits.

Comparison between and integration across disorders

All discussed disorders exhibit symptoms that signify a failure to inhibit certain impulses or responses. Response inhibition tasks therefore provide a very good operationalization to study the neural correlates of some dysfunctions contributing to the symptomatology of these disorders. From the above reviewed literature we can conclude that, overall, patients with PD and disorders within the impulsive-compulsive spectrum exhibit deficits in response inhibition concomitant with alterations in the task-related brain activity. Whether these brain areas are hypo- or hyperactivated compared with matched healthy controls depends largely on the complexity of the task. In general we can state that patients compensate behavior by recruiting additional inhibition-related brain areas, explaining why behavioral performance is often normal, but only during less complex tasks (e.g. the Flanker task and the Simon task). With increasing task demand (e.g. the GO/no-go and the Stop signal task), these compensational mechanisms fail and patients start to show behavioral impairments and decreased inhibition-related neural circuit activity. This phenomenon has also been observed in healthy subjects (Sebastian *et al.* 2013a; Sebastian *et al.* 2013b), although they can 'endure' tasks with higher demands before overstressing the inhibition network and concomitant decrements in performance. In other words, patients with all discussed disorders, including PD, seem to exhibit performance impairments and failure of compensatory activation at a lower task load than healthy controls. This has also been observed in OCD patients and their siblings and adult patients with ADHD while performing a working memory task such as the N-Back (de Vries *et al.* 2014; Ko *et al.* 2013). Figure 7.2 illustrates this as a shift to the left of an inverse U-shape relation between task load and inhibition-related activity. This shift in compensatory abilities does not have to be specific for the discussed disorders but may also apply to others or even natural aging (Sebastian *et al.* 2013a).

The actual neurobiological mechanism for this shift is, unfortunately, less apparent and may involve (interactions between) electrophysiological anomalies, neurotransmitter dysfunction, genetic variance, etc. A prime candidate for the

cause of the shift might by dysfunction of dopamine signaling. Dopamine is the major neuromodulator in the CSTC circuits and can either facilitate or inhibit their activation depending on the activation of their different receptor subtypes and dopamine concentrations (Alexander *et al.* 1986; Vriend *et al.* 2014c). As reviewed above, the CSTC circuits seem to be important for response inhibition (Aron 2011) and are also involved in the pathophysiology underlying the dysfunctions related to the symptomatology of PD and the disorders within the impulsive-compulsive spectrum. Whether or not dopamine is primarily involved in the pathophysiology of these disorders is still under debate, with some of the above reviewed studies showing clear associations, while others do not. Nevertheless, current evidence suggests that PD and ADHD can be seen as a hypodopaminergic disorder, whereas OCD, TTM and TS can be regarded as hyperdopaminergic disorders (Buse *et al.* 2013). This is also consistent with the currently available pharmacological treatments, whose neurobiological mechanism is thought to rely on restoring dopamine to physiological levels (Abi-Dargham and Laruelle 2005; Gerlach *et al.* 2013). Even SSRIs and tricyclic antidepressants, the first line pharmacological treatment of OCD, may normalize dopamine levels by upregulation of serotonin signaling, that has an inhibitory effect on dopamine (Boureau and Dayan 2010). Figure 7.3 provides a schematic representation of the proposed relation between dopamine levels and inhibitory control. This relation is similar to the inverse U-shaped relation proposed for dopamine levels and working memory function (Cools and D'Esposito 2011).

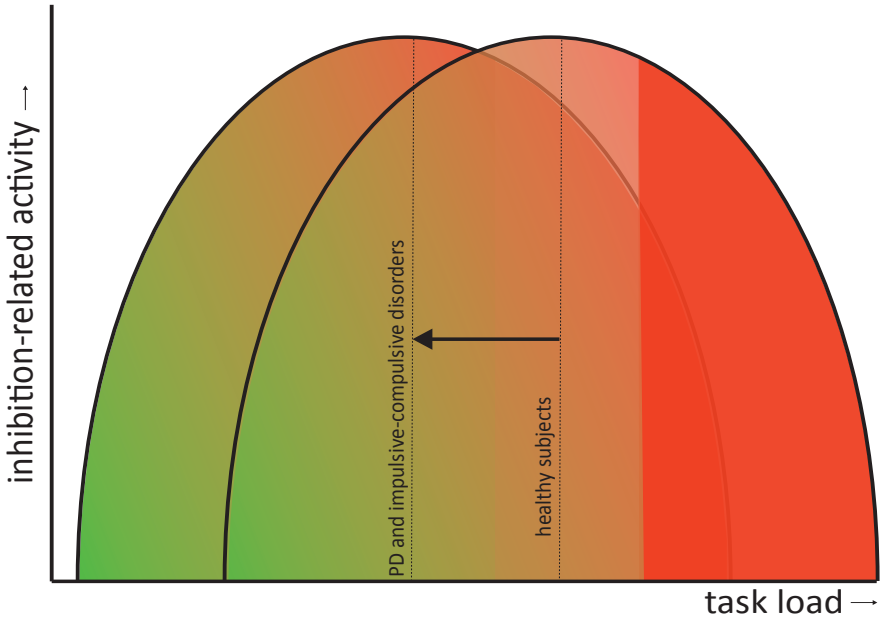
The proposed relation obviously does not provide the full story and is merely intended as a framework to understand some of the findings discussed in this review. Dopamine has differential effects in the prefrontal cortex and striatum, different firing modes (i.e. tonic and phasic) and highly complex interactions with other neurotransmitter systems, including the serotonin, noradrenalin and glutamate system, and even hormones, such as estrogens (Boureau and Dayan 2010; Cools and D'Esposito 2011; de Bartolomeis *et al.* 2013), which prohibits a clear understanding of the influence of these neurotransmitters on brain activity and behavior.

In short, the functional and behavioral deficits in response inhibition in PD and impulsive-compulsive spectrum disorders can be conceptualized as a shift in the relation between task demands and inhibition-related neural circuit activity. What causes this shift and what could thereby underlie the symptoms of these disorders is currently unknown, although we postulate that dopamine plays a critical role.

Conclusions and future directions

The aim of this review was to provide an overview of the studies that examined the neural, pharmacological and genetic substrates of inhibitory impairment of disorders within the impulsive-compulsive spectrum, with a focus on ICD, OCD, ADHD, TS and TTM. We additionally used PD as a model disease for CSTC circuit dysfunction, to show that the CSTC circuits are important for response inhibition and that some patients develop clinically significant deficits in impulse control (i.e. ICD) after commencing dopamine replacement therapy. We have shown that functionally and behaviorally impaired response inhibition is a shared characteristic among these disorders and may underlie at least some of the dysfunctions related to the symptomatology of the disorders. Neuroimaging studies suggest that inhibition-related brain areas are mostly hypoactivated in PD, ADHD and OCD (although dependent on the task load), while studies in TS have provided mixed results. To our knowledge, no study has yet been published on the neural correlates of response inhibition in TTM. Dopamine and serotonin signaling seems to be important for response inhibition and dysfunction of these neurotransmitters has been frequently observed in disorder within the impulsive-compulsive spectrum. Nevertheless, almost all imaging studies on neurotransmitters have been performed in patients that received (chronic) pharmacotherapy which may have influenced the scan directly, due to competition of the drug with a radioligand for a specific binding site, or indirectly because the brain adapts to the pharmacological effects (Wang *et al.* 2013). For a better understanding of the pathophysiology of the disease itself and the identification of novel treatment targets, more studies are needed in medication-naïve patients. Prospective follow-up of these patients after commencing treatment can subsequently provide insights into the effect of treatment on response inhibition impairments and its relation to disorder-specific symptoms. Lastly, there is a relative lack of studies that compare the pathophysiology of inhibitory deficits across related mental disorders. Such studies allow the identification of common as well as specific disease biomarkers of impulsivity and compulsivity symptoms.

Figure 7.2 (next top page) – Shift in the inverted U-shaped relation between task load and inhibition-related activity. Inhibition-related activity gradually increases with task load (green to red gradient). However, when task demands become too high the compensatory activity starts to fail and behavioral performance becomes impaired (solid red). In obsessive-compulsive and related disorders performance impairments and failure of compensatory activation occur at a lower task load than in healthy controls (shift of the inverted U-shaped curve to the left).



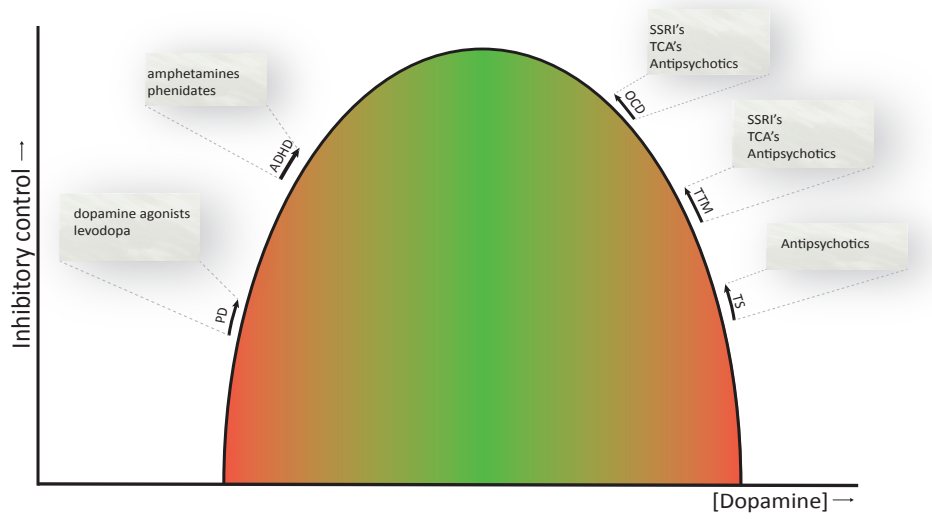


Figure 7.3 – Inverted U-shaped relation between dopamine levels and inhibitory control. The ability to control behaviors, impulses and urges is influenced by dopamine and both reduced and increased dopamine levels (green to red gradient) have a detrimental effect on inhibitory control. Current evidence suggest that ADHD is a hypodopaminergic disorder, while OCD, TTM and TS are considered hyperdopaminergic disorders. Inhibitory deficits are also evident in patients with Parkinson's disease, a prototypical hypodopaminergic disease. Pharmacotherapeutics used to treat the symptoms of these disorders are listed and are thought to normalize dopamine levels and thereby ameliorate response inhibition. abbreviations: PD = Parkinson's disease, ADHD = attention deficit hyperactivity disorder, OCD = obsessive-compulsive disorder, TTM = trichotillomania, TS = Tourette's syndrome.

Table 7.1 – Overview of studies that have used interference control or motor response inhibition tasks in Parkinson's disease.

Study	Task	Participants	Med?	IC or RI behavior	Remarks
Wylie *et al.* 2009	Flanker	28 PD 17 HC	yes	↓	PD patients made more errors than healthy controls
Willemssen *et al.* 2008	Flanker	20 PD on/off 20 HC	yes	=	No differences between the on and off state
Falkenstein *et al.* 2006	Flanker	15 PD 15 HC	yes	=	
Cagigas *et al.* 2007	Flanker	20 PD 15 HC	yes	=	
Praamstra *et al.* 1999	Flanker	10 PD 9 HC	yes	↓	
Praamstra *et al.* 1998	Flanker	7 PD 7 HC	yes	↓	
Praamstra and Plat 2001	Simon	8 PD 9 HC	yes	=	variability of response times was relatively larger for control subjects in the compatible condition
Wylie *et al.* 2010	Simon	52 PD 30 HC	yes	=	Accuracy was also comparable between groups.
Fielding *et al.* 2005	Simon	10 PD 10 HC	yes	↓	
Schmiedt-Fehr *et al.* 2007	Simon	11 PD 22 HC	yes	↓	Studies employed two healthy control groups: a young group and a age-matched senior group
Alegret *et al.* 2001	Stroop	14 PD	yes		Negative correlation between ventricular enlargement and Stroop performance.
Filoteo *et al.* 2014	Stroop	51 PD 39 HC	yes	↓	PD patients completed less items in 45 s. Stroop performance was positively correlated with volume of the inferior frontal gyrus, putamen and entorhinal cortex (FreeSurfer).
Duthoo *et al.* 2013	Stroop	9 PD on/off	yes	=	No difference in interference effect between medication states

Bonnin *et al.* 2010	Stroop	18 PD 18 HC	yes	=	
Dujardin *et al.* 1999	Stroop	17 PD 17 HC	yes	↓	
Rustamov *et al.* 2013	Stroop	20 PD 20 HC	yes	=	
Vandenbossche *et al.* 2012	Stroop	28 PD 14 HC	yes	=	
Woodward *et al.* 2002	Stroop (modified)	30 PD 34 HC	yes	=	Interference effects increased in PD when the demands of the task increased.
Beste *et al.* 2009	Go/No-go	15 PD 15 HC	yes	↓	
Bokura *et al.* 2005	Go/No-go	13 PD 14 HC	yes	↓	Higher omission and commission error rates in PD but similar reaction times for correct responses
Baglio *et al.* 2011	Go/No-go	15 PD 11 HC	yes	=	During performance of the task, PD patients showed increased activation of the prefrontal cortex and basal ganglia, and decreased activation of the occipital cortex compared with healthy controls. There were no behavioral differences.
Farid *et al.* 2009	Go/No-go	9 PD on/off 9 HC	yes	=	No difference between PD patients and healthy controls regardless of medication status. No difference between PD patients on vs off medication. PD patients off medication showed increased activation of the superior parietal cortex, superior temporal cortex and bilateral caudate compared with healthy controls. Activation of the superior temporal cortex and bilateral caudate was higher during the off than on state.
O'Callaghan *et al.* 2013b	Go/No-go	25 PD 15 HC	yes	↓	Performance decrements during the Go/No-go task were associated with decreased volume of the right nucleus accumbens (Voxel-based Morphometry).
Gauggel *et al.* 2004	Stop	32 PD 31 HC	yes	↓	
Nombela *et al.* 2014	Stop	30 PD 30 HC	yes	↓	

Study	Task	Participants	Med?	IC or RI behavior	Remarks
Obeso *et al.* 2011a	Stop	18 PD 29 HC	yes	↓	
Obeso *et al.* 2011b	Stop	17 PD on/off 16 HC	yes	↓	No difference between PD patients on vs off medication.
Vriend *et al.* 2015	Stop	21 PD 37 HC	no	=	Slightly increased SSRT in de novo PD compared with healthy controls. Reduced activation of the bilateral inferior frontal gyrus and left inferior parietal lobule in PD patients versus healthy controls during performance of the task. Activation of the right inferior frontal gyrus correlated negatively with motor symptom severity and positively with ventral striatal dopamine transporter availability.
Ye *et al.* 2014b	Stop	21 PD 20 HC	yes	↓	Decreased activation of the right inferior frontal gyrus in PD patients compared with healthy controls during performance of the task. Citalopram enhanced right inferior frontal gyrus activation but only in the more advanced stages of PD. Patients with a greater structural connectivity between the frontal lobe and basal ganglia showed a higher reduction in SSRT in response to citalopram.
Ye *et al.* 2014a	Stop	21 PD 20 HC	yes	↓	Decreased activation of the right inferior frontal gyrus in PD patients compared with healthy controls during performance of the task. PD patients also showed decreased functional connectivity between the right inferior frontal gyrus and striatum. Atomoxetine enhanced right inferior frontal gyrus activation and functional connectivity but had no effect on overall behavioral performance.

↓ reduced interference control or response inhibition in PD vs HC; = no between-group differences. Abbreviations: med = medication, IC = interference control, RI = response inhibition, PD= Parkinson's disease, HC= healthy controls.

Table 7.2 – Overview of fMRI studies that have used interference control tasks in obsessive-compulsive disorder.

Study	Task	Age group	Participants	Medication & co-morbidities	Contrast	Findings in OCD patients
Fitzgerald *et al.* 2005	Flanker	Adults	8 OCD 7 HC	Three patients were treated with SSRI's, one with benzodiazepines and one received antipsychotic medication. Three patients met criteria for depression, two for dysthymia. No severe medical conditions, neurological disorder or head injury.	E > Corr IC > C	↑ Rostral ACC (+ correlation with severity of symptoms) ↓ R. pre-SMA ↑ Bilateral caudate nucleus
Huyser *et al.* 2011	Flanker	Children/ Adolescents	25 OCD 25 HC	Medication-free for at least two weeks prior to participation. Forty-eight percent of patients had co-morbid anxiety disorder, 12% co-morbid affective disorders, 12% ADHD / ODD and 8% tic disorders	E > Corr IC > C	↑ ACC, insula ↑ Bilateral insula
Nakao *et al.* 2005a	Stroop	Adults	24 OCD 14 HC	Medication-free for at least two weeks prior to participation. No co-morbid axis-I disorders, no severe medical condition, neurological disorder, head injury or substance abuse	IC > C	↑ R. frontal lobe ↓ Bilateral ACC, temporal lobe, r. caudate nucleus
Nabeyama *et al.* 2008	Stroop	Adults	11 OCD 19 HC	Medication-free for at least two weeks prior to participation. Co-morbid disorders unreported	IC > C	↓R. ACC, r. cerebellum
Woolley *et al.* 2008	Motor Stroop	Children/ Adolescents	10 OCD 9 HC	Eight patients treated with an SSRI, five treated with CBT. No co-morbid axis-I disorder, neurological disorder, head injury, severe medical condition	IC > C	↓ R. middle temporal gyrus, bilateral cerebellum
Page *et al.* 2009	Motor Stroop	Adults	10 OCD 11 HC	Medication-free. Two patients met criteria for dysthymic disorder, three previously met criteria for depression and one previously met criteria for alcohol dependence	IC > C	↑ L. Cerebellum, l. posterior cingulate ↓ Bilateral Precuneus, r. temporal gyrus, l. temporo-parietal junction

Study	Task	Age group	Participants	Medication & co-morbidities	Contrast	Findings in OCD patients
Nakao *et al.* 2009	Stroop	Adults	17 OCD : duration of illness < 10 years 15 OCD : duration of illness > 10 years 16 HC	Medication-free for at least two weeks prior to participation. No co-morbid axis I-disorder, no severe medical condition, neurological disorder, head injury or substance abuse.	IC > C	↓ R. caudate, cerebellum in patients with disease duration < 10 years compared with patients with longer disease duration and controls
Schlosser *et al.* 2010	Stroop	Adults	21 OCD 21 HC	Medication-free for at least two days prior to participation. No co-morbid axis-I disorder, no psychosis or neurological disorder	IC > C IC	↑ Bilateral DLPFC ↑ Bilateral superior frontal gyri, dorsal ACC, left pre-central gyrus, right superior parietal lobe and right inferior parietal
van den Heuvel *et al.* 2005	Stroop	Adults	18 OCD 19 controls	Medication-free for at least 4 weeks prior to participation. No neurological illness, other psychiatric disorders	IC > C	↑ R. precuneus, L. parahippocampal gyrus, L. rostral brainstem
Viard *et al.* 2005	Conflict	Adults	12 OCD 15 HC	Eleven patients were treated with SSRI's, one also with a TCA. No co-morbid disorders, no severe medical condition, neurological disorder or head injury.	IC > C	No difference in brain activation
Marsh *et al.* 2014	Simon	Adults	22 OCD 22 HC	Medication-free. Five patients had a lifetime history of depression	IC > C	↑ R. IFG, Insula and putamen
Rubia *et al.* 2011a	Simon	Children/ Adolescents	10 OCD 20 HC	Eight patients were treated with SSRI's; five patients with CBT. No co-morbid psychiatric disorders, no history of learning disabilities or substance abuse	IC > oddball	↓ R. pre-SMA, ACC, superior parietal cortex

Abbreviations: ADHD: Attention-deficit hyperactivity disorder: C: congruent trials; CBT: cognitive behavioral therapy; corr: correct trials; DLPFC: dorsolateral prefrontal cortex; E: error trials; f: female; IC: incongruent trials; ODD: oppositional defiant disorder; OFC: orbitofrontal cortex; SMA: supplementary motor area; SSRI: selective serotonin re-uptake inhibitor; STG: superior temporal gyrus; TCA: tricyclic anti-depressant.

Table 7.3 – Overview of fMRI studies that have used response inhibition paradigms in obsessive-compulsive disorder.

Study	Task	Age group	Participants	Medication & co-morbidities	Contrast	Findings in OCD patients
Maltby *et al.* 2005	Go/No-go	Adults	11 OCD 11 HC	Medication free; OCD is primary diagnosis, six patients met criteria for one other axis I disorder. No psychosis, neurological disorder, head injury, substance abuse	FS > Go SS > Go	↑ Lateral prefrontal cortex, ACC, lateral OFC, caudate, thalamus during failed and successful inhibition
Roth *et al.* 2007	Go/No-go	Adults	12 OCD 14 HC	Six patients treated with an SSRI; Two patients met criteria for depression, one for social phobia. No neurological disorder, head injury, severe medical condition or substance abuse	No go > Go	↓ R. IFG, R. middle frontal gyrus
Woolley *et al.* 2008	Stop	Children/ Adolescents	10 OCD 9 HC	Eight patients treated with an SSRI, five treated with CBT; No comorbid axis-I disorder, neurological disorder, head injury, severe medical condition	SS > FS FS > Go	↓ R. OFC, thalamus, basal ganglia ↓ DLPFC, temporal lobe activation
Page *et al.* 2009	Go/No-go	Adults	10 OCD 11 HC	Medication free; Two patients met criteria for dysthymic disorder, three previously met criteria for depression and one previously met criteria for alcohol dependence	No go > Go No go > Go	↑ VMPFC, posterior cingulate, premotor cortex, cerebellum ↓ OFC, DLPFC, ACC, putamen, caudate, hippocampus, thalamus
Rubia *et al.* 2010	Stop	Adolescents	10 OCD 20 HC	Patients received treatment and were in partial remission; No major psychiatric disorders, substance abuse, learning disabilities	SS > Go FS > Go	↓ R. OFC (+ correlation with improvement of symptoms) ↓ Left middle frontal gyrus
de Wit *et al.* 2012	Stop	Adults	41 OCD 14 siblings 37 HC	Medication free; Twenty-two patients met diagnostic criteria for another axis-I disorder. No psychosis, neurological illness, severe medical conditions.	SS > SG SS > SG	↑ Pre-SMA (also in unaffected siblings) ↓R. IFG and r. inferior parietal cortex

Study	Task	Age group	Participants	Medication & co-morbidities	Contrast	Findings in OCD patients
Kang *et al.* 2013	Stop	Adults	18 OCD 18 HC	Medication free; No major psychiatric disorders, psychosis, neurological illness, substance abuse, depression, mental retardation	SS > Go SS > Go	↑ Bilateral superior parietal cortex, cerebellum, R. parahippocampal cortex ↓R. putamen, L. precentral gyrus, R. fusiform cortex, bilateral caudate and temporal lobe; R. middle occipital cortex, L. angular gyrus, L. cerebellum, R. cingulate cortex

Abbreviations: ACC: anterior cingulate cortex; CBT: cognitive behavioral therapy; DLPFC: dorsolateral prefrontal cortex; f: female; FS: failed stop; IFG: inferior frontal gyrus; MTL: middle temporal lobe; OFC: orbitofrontal cortex; SS: successful stop; SSRI: selective re-uptake inhibitor; VMPFC: ventromedial prefrontal cortex.

Table 7.4 – Overview of fMRI studies that have used interference control tasks and response inhibition tasks in patients with Tourette's syndrome.

Study	Task	Age group	Participants	Medication & co-morbidities	Contrast	Findings in TS patients
Hershey *et al.* 2004	Go/No-go	Adults	8 TS 10 HC	Medication-free (< 24 hours); Two patients with comorbid OCD, four patients with comorbid ADHD	Task > fixation	No differences in brain activation during task performance compared to controls
Raz *et al.* 2009	Simon	Children/ Adults	42 TS 37 HC	Medication use unreported; One patient with comorbid OCD and one patient with comorbid OCD & ADHD	IC > C	↑ activation of frontal-striatal regions with age in TS
Marsh *et al.* 2007	Stroop	Children/ Adults	66 TS 70 HC	Thirty-eight patients used psychoactive medication (haloperidol/risperidone/SSRIs) Twenty-five patients with comorbid ADHD; eight with comorbid ADHD and five with comorbid OCD/ADHD	IC > C	↓ deactivation of the mesial PFC and ventral ACC with age in TS patients Activation of the R. IFG, L. DLPFC, lenticular nucleus and thalamus associated with better performance in controls and poorer performance in TS patients

Abbreviations: ACC: anterior cingulate cortex; C: congruent; DLPFC: dorsolateral prefrontal cortex; IC: incongruent; IFG: inferior frontal gyrus; f: female; L: left; PFC: prefrontal cortex; R: right; SSRI: selective serotonin reuptake inhibitor.

Table 7.5 – Overview of fMRI studies that have used interference control tasks in patients with Attention-deficit hyperactivity disorder

Study	Task	Age group	Participants	Medication & co-morbidities	Contrast	Findings in ADHD patients
Vaidya *et al.* 2005	Modified Flanker	Children	10 ADHD 10 HC	Medication naïve or medication free (36 hours); Symptoms of ODD present in seven patients; symptom of CD reported in two children	IC> N	↓ L. IFG
Vasic *et al.* 2014	Modified Flanker	Adults	14 ADHD 12 HC	Medication free (4 days) No comorbid psychiatric disorders, substance abuse, neurological disorders, learning disabilities	Error > correct	↓ L. IFG during error processing
Cubillo *et al.* 2011	Simon	Adults	11 ADHD 15 HC	Medication-naive; Three patients had ADHD symptoms, but did not meet all criteria for ADHD. Comorbid disorders: one patient with anxiety, three with mood disorders, one with CD and two with substance abuse	IC > C	↓ L. IFG/OFC, L. medial frontal cortex, L. ACC, L. caudate, L. premotor cortex
Rubia *et al.* 2011b	Simon	Children	12 ADHD 13 HC	Medication-naïve; One patient met criteria for ODD/CD	IC > oddball	↓R. IFG, R. IPC, L. VMPFC, basal ganglia, thalamus, R. SMA/ACC/posterior cingulate, L. superior/middle temporal/occipital cortex
Rubia *et al.* 2011a	Simon	Children	18 ADHD 20 HC	Medication-naïve; One patient met criteria for CD	IC > oddball	↓ R. SMA/ACC/superior parietal lobe, R. IPC
Sebastian *et al.* 2012	Simon	Adults	20 ADHD 24 HC	Unmedicated or medication-free (2 months); Eight patients with current comorbid disorders (dysthymia, anxiety disorders, substance abuse, personality disorders)	IC > C	↓ R. precentral gyrus, L. paracentral lobe, L. middle cingulate cortex, bilateral superior temporal gyrus, L. middle temporal gyrus, R. temporal pole, R. insula, R. pallidum
Bush *et al.* 1999	Stroop	Adults	8 ADHD 8 HC	Medication-free (> 48 hours); No comorbid psychiatric disorders, neurological disorders, learning disability, medical illness	IC > N	↓ACC (cognitive division)
Smith *et al.* 2006	Stroop	Children / Adolescents	17 ADHD 18 HC	Medication naïve; Five patients with comorbid conduct disorder	IC > oddball	No significant differences

Banich *et al.* 2009	Stroop	Adults	23 ADHD 23 HC	Medication-free (24 hours); No comorbid psychiatric disorders, learning disability, history of seizures or head injury	IC > N IC > C	↓ L. supramarginal gyrus ↑ R. cuneus, R. middle frontal gyrus
Peterson *et al.* 2009	Stroop	Adoles-cents	16 ADHD 20 HC	Medication-free; Five patients had comorbid disorders (ODD, depres-sion, anxiety disorders, phobias)	IC > C	↓ L. ACC, L. insula, R. precune-us, thalamus, caudate ↑ R. hippocampus, R. superior frontal gyrus, L. ACC
Burgess *et al.* 2010	Stroop	Adults	20 ADHD 23 HC	Medication free (24 hours); No comorbid psychiatric or learning disorder	IC > N	↑ R. superior frontal gyrus

Abbreviations: ACC: anterior cingulate cortex; C: congruent trials; CD: conduct disorder; IC: incongruent trials; IFG: inferior frontal gyrus; IPC: inferior parietal cortex; f: female; L: left; N: neutral trials; ODD: oppositional defiance disorder; OFC: orbitofrontal cortex; R: right; SMA: supplementary motor area; VMPFC: ventromedial prefrontal cortex.

Table 7.6 – Overview of fMRI studies that have used response inhibition tasks in patients with Attention-deficit hyperactivity disorder.

Study	Task	Age group	Participants	Medication & co-morbidities	Contrast	Findings in ADHD patients
Rubia *et al.* 1999	Stop	Adoles-cents	7 ADHD 9 HC	Medication-naïve or medication-free (1 week); No comorbid psychiatric disorder (except con-duct disorder) or neurological disease	Stop > Go	↓ R. IFG, R. MPFC, L. caudate
Rubia *et al.* 2005b	Stop	Adoles-cents	16 ADHD 21 HC	Medication-naïve; Five patients with conduct disorder. No neuro-logical disease, substance abuse or previous treatment with stimulants	SS > FS FS > Go	↓ R. frontotemporal pole, R. OFC, R. superior temporal lobe ↓ R. Posterior cingulate/precu-neus
Pliszka *et al.* 2006	Stop	Children/ Adoles-cents	9 treated ADHD 8 medication-free ADHD 15 HC	Medication-naïve or medication free; No psychiatric disorder (except ODD), substance abuse, alcohol abuse	Stop > Go	↑ R. DLPFC
Cubillo *et al.* 2010	Stop	Adults	11 Adults with persistent ADHD 14 HC	Medication-naïve; Seven subjects with Axis I disorders (anxiety, depression, conduct disorder, substance related disorders). No neurological abnormalities, treat-ment with stimulants	SS > Go FS > Go	↓ L. IFG/insula, R. IFG/insula, striatum, thalamus, R. premotor cortex, bilateral SMA/ACC ↓R. IFG/insula, thalamus, striatum
Passarotti *et al.* 2010	Stop	Children/ Adoles-cents	11 ADHD 15 HC	Medication-naïve or medication-free (1 week); No comorbid psychiatric conditions, neurolog-ical disorders, learning disabilities, history of substance abuse	Stop > Go	↑ L. caudate, R. caudate tail, L. cerebellum ↓ R. middle, superior and inferior frontal gyrus, L. superior and inferior frontal gyrus; L. superior temporal gyrus
Rubia *et al.* 2011b	Stop	Children	12 ADHD 13 HC	Medication-naive; One patient with comorbid ODD/CD. No psychi-atric disorders, learning disabilities, neurological disorders, epilepsy, substance abuse, treatment with stimulants	FS > Go SS > Go	↓ L. IFG, Pre-SMA, R. premotor cortex, bilateral thalamus, R. IPC, L. posterior cingulate, L. precuneus, cerebellum ↓ Bilateral IFG, bilateral pre-SMA, thalamus, bilateral ACC, R. IPC/precuneus/posterior cingulate, cerebellum

Sebastian *et al.* 2012	Stop	Adults	20 ADHD 24 HC	Unmedicated or medication-free (2 months); Eight patients with current comorbid disorders (dysthymia, anxiety disorders, substance abuse, personality disorders)	Stop > Go SS > FS	↓ R. Pallidum ↓ L.IFG, bilateral putamen, R. caudate, L. insula, L. pallidum.
Durston *et al.* 2003	Go/ No-go	Children	7 ADHD 7 HC	Medication-free (1 day) ; Comorbid disorders not reported	No go > Go	↓ L. caudate ↑ R. Middle and superior frontal gyrus, L. IPC, bilateral posterior cingulate/precuneus , R. superior temporal gyrus
Tamm *et al.* 2004	Go/ No-go	Adoles-cents	10 ADHD 12 HC	Medication-naïve and medication free (18 hours); Controls had no family history of psychiatric disorders, no neurological or developmental disorders.	No go > Go	↓ R. ACC/SMA, R. superior and middle frontal gyrus ↑ L. superior/middle/inferior temporal gyrus,
Schulz *et al.* 2004	Go/ No-go	Adoles-cents	10 individuals with childhood ADHD diagnosis 9 HC	Medication-free (6 months); One patient with conduct disorder	No go > Go	↑ Bilateral IFG, bilateral middle frontal gyrus, L. ACC, bilateral IPC, right precuneus ↓ R. precentral gyrus, R. inferior temporal gyrus, L. hippocampus, bilateral cerebellum
Booth *et al.* 2005	Go/ No-go	Children	12 ADHD 12 HC	Medication-free (2 days); No comorbid psychiatric disorders, neurological disorders, substance abuse, visual or hearing impairment	No go > Go	↓ R. IFG, R. superior frontal gy-rus, medial frontal gyrus, bilateral caudate, R. amygdala, thalamus, fusiform gyrus, L. cuneus, L. globus pallidum
Smith *et al.* 2006	Go/ No-go	Children / Adoles-cents	17 ADHD 18 HC	Medication naïve; Five patients with comorbid conduct disorder	No go > oddball go	↓ L. rostral mesial frontal cortex

Study	Task	Age group	Participants	Medication & co-morbidities	Contrast	Findings in ADHD patients
Suskauer *et al.* 2008	Go/ No-go	Children/ Adoles-cents	25 ADHD 25 HC	Medication-free (2 days); Eleven patients also met criteria for ODD, five patients met criteria for specific phobia, two controls met criteria for specific phobia	No go	↑ R. precentral gyrus ↓R. ACC, L. precentral gyrus, L. putamen, R. temporal-parietal junction, R. fusiform gyrus, L. precuneus, L. posterior cingulate, L. cerebellum
Dibbets *et al.* 2009	Go/ No-go	Adults	16 ADHD 13 HC	Medication-free (24 hours); Two patients with depressive symptoms, one reported OCD symptoms, two reported learning disabilities and one reported substance abuse.	Go No go	↑ R. middle frontal gyrus, L. IFG ↑ L. IFG, R. putamen
Dillo *et al.* 2010	Go/ No-go	Adults	15 ADHD 15 HC	Medication-free (3 weeks); No comorbid psychiatric diagnosis, substance abuse, neurological disorders.	No go > Go	↑ Bilateral inferior/superior parietal lobe, left inferior/middle occipital gyrus
Kooistra *et al.* 2010	Go/ No-go	Adults	10 ADHD 10 HC	Medication-naive; Two patients in partial remission, no comorbid psychiatric disorders, neurological disorders, cognitive impairment, motor disabilities	No go > Go	↑ R. supramarginal gyrus, R. ACC
Mulligan *et al.* 2011	Go/ No-go	Adults	12 ADHD 12 HC	Medication free (> 2 days) No comorbid Axis I diagnosis, history of learning disability, history of neurological disorders, alcohol or substance dependence, use of stimulants	No go	↓ R. Pre-SMA, bilateral IPC, L. precentral gyrus, R. frontal eye fields, L. precuneus
Spinelli *et al.* 2011	Go/ No-go	Children	13 ADHD 17 HC	Medication free (2 days) Three patients had comorbid ODD, one a specific phobia.	Post error > Post correct	↑ R. superior frontal gyrus, L. medial frontal gyrus, R. cingulate gyrus, R. postcentral gyrus, R. inferior/middle temporal gyrus
Sebastian *et al.* 2012	Go/ No-go	Adults	20 ADHD 24 HC	Unmedicated or medication-free (2 months); Eight patients with dysthymia, anxiety disorders, substance abuse	Stop > Go	↓ R. Caudate

Abbreviations: ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; FS: failed stop trials; IFG: inferior frontal gyrus; IPC: inferior parietal cortex; f: female; L: left; MPFC: medial prefrontal cortex; ODD: oppositional defiance disorder; OFC: orbitofrontal cortex; Pre-SMA: pre-supplementary motor area; R: right; SMA: supplementary motor area; SS: successful stop trials.