The Cognitive Neuroscience of Response Inhibition: Relevance for Genetic Research in Attention-Deficit/Hyperactivity Disorder

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Psychological functions that are behaviorally and neurally well specified may serve as endophenotypes for attention-deficit/hyperactivity disorder (ADHD) research. Such endophenotypes, which lie between genes and symptoms, may relate more directly to relevant genetic variability than does the clinical ADHD syndrome itself. Here we review evidence in favor of response inhibition as an endophenotype for ADHD research. We show that response inhibition– operationalized by Go/NoGo or Stop-signal tasks–requires the prefrontal cortex (PFC), in particular the right inferior frontal cortex (IFC); that patients with ADHD have significant response inhibition deficits and show altered functional activation and gray matter volumes in right IFC; and that a number of studies indicate that response inhibition performance is heritable. Additionally, we review evidence concerning the role of the basal ganglia in response inhibition, as well as the role of neuromodulatory systems. All things considered, a combined right IFC structure/function/response inhibition phenotype is a particularly good candidate for future heritability and association studies. Moreover, a dissection of response inhibition into more basic components such as rule maintenance, vigilance, and target detection may provide yet better targets for association with genes for neuromodulation and brain development.

Key Words: Attention-deficit/hyperactivity disorder, Stop-signal response inhibition, Go/NoGo, inferior frontal cortex, basal ganglia, brain development

Converging evidence from family, twin, and adoption studies suggests there is a robust genetic component to the etiology of attention-deficit/hyperactivity disorder (ADHD) (Castellanos and Tannock 2002). Moreover, molecular genetic studies have begun to find small but significant associations between variability at particular genetic loci (e.g., the dopamine D4 receptor gene, DRD4) and ADHD. However, such work represents only the beginning of a difficult process of specifying the genetic contribution in detail. Part of the difficulty is that ADHD, like other psychiatric disorders, is likely mediated by many genes acting in concert, with each particular gene only exerting a small effect (Comings 2001).

A recent approach is to focus less on the association between genes and symptom-based diagnostic categories such as ADHD and more on intermediate phenotypes (known as endophenotypes), which lie between the genes and symptoms (see Almasy and Blangero 2001, for the rationale for endophenotypes in psychiatric disease). In neuropsychiatric disorders, such endophenotypes may include specific cognitive processes (Winterer and Goldman 2003). These endophenotypes may serve as markers for risk of psychiatric pathology in the same way as, to use a well-worn example, cholesterol levels serve as a marker for heart disease. Identifying cognitive markers that are probabilistically related to ADHD pathology (even without manifest ADHD symptoms) is helpful for identifying genetic factors.

There have been hundreds of studies of the cognitive basis of ADHD, and theoretical descriptions of the "core" deficit abound. These include "executive function," "delay aversion," and "activation/arousal" accounts (see reviews by, for example, Castellanos and Tannock 2002; Nigg 2001; Sergeant et al 2003; Sonuga-Barke 2002). Identifying a cognitive endophenotype requires finding a measure that is: 1) capable of distinguishing patients with ADHD from healthy control subjects, 2) anchored in known neural systems, and 3) heritable in the sense that individual differences in cognition can be attributed to individual genetic differences. Multiple studies (reviewed below) suggest that response inhibition (for Go/NoGo and Stop-signal tasks) is one of several task measures that distinguish ADHD patients from healthy control subjects (see Castellanos and Tannock 2002, for a discussion of other measures such as working memory and temporal processing). Here we argue that response inhibition is a particularly good candidate endophenotype for ADHD: inhibiting a prepotent response is associated with activity in specific brain regions in healthy subjects, damage to those regions results in response inhibition deficits, and neural dysfunction or pathology in these regions is evident in ADHD. By endorsing response inhibition in this way, we do not mean to imply that it is necessarily the core deficit in ADHD (cf. Barkley 1997) or even the most suitable or reliable measure for all purposes (e.g., it may only pertain to one of several subtypes of ADHD). Nor do we mean to imply that response inhibition is a discrete cognitive function–indeed, we believe that measures of response inhibition (such as speed of stopping or number of failures to stop) represent a combination of cognitive processes such as sustained attention, target detection, and rule maintenance. Nevertheless, we argue that response inhibition is highly promising as a candidate endophenotype for future genetic studies of ADHD.

Response Inhibition as a Measure of Executive Control

Executive control consists in high-level cognitive functions instantiated by interactions between the prefrontal cortex (PFC) and posterior cortical and subcortical foci (Miller and Cohen 2001). These high-level functions, which optimize and schedule, for example, the lower-level motor and perceptual systems, are frequently operationalized by measures of task switching, reversing stimulus-response rules, shifting categories, or suppressing prepotent responses. Although the requirement to suppress a prepotent response may be present in multiple task contexts

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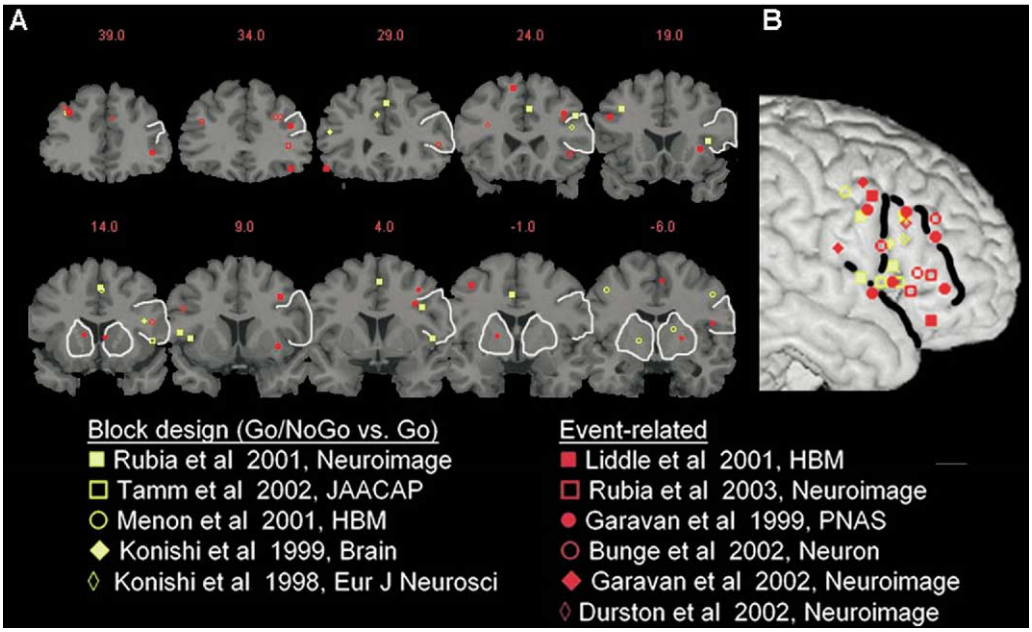

Figure 1. Meta-analysis of response inhibition functional MRI studies in healthy volunteers (please see online article for color). All frontal and basal ganglia activation foci in the range $-7 < y < 41$ (Talaraich coordinates) reported in 11 studies are plotted on **(A)** coronal slices and **(B)** lateral/saggital view of a standard structural template. Yellow activations reflect blocked Go versus Go/NoGo studies (Konishi et al 1998, 1999; Menon et al 2001; Rubia et al 2001; Tamm et al 2002); red activations reflect event-related studies contrasting Go with NoGo trials (Bunge et al 2002; Durston et al 2002; Garavan et al 1999, 2002; Liddle et al 2001) or using the Stop-signal paradigm (Rubia et al 2001, 2003). Although activations fall within dorsolateral, ventrolateral, medial, and premotor (precentral gyrus), it is evident that: 1) more frontal activations fall within the right hemisphere, 2) most frequently the activations within the right frontal region fall within the inferior frontal (ventrolateral) region of the prefrontal cortex, and 3) only a few studies report basal ganglia activation. On the sagittal view, the sulcal boundaries of the inferior frontal gyrus are shown.

such as task switching, Stroop interference, and Wisconsin Card Sort Testing (Aron et al 2004b; Friedman and Miyake 2004), it is most clearly measured by Go/NoGo and Stop-signal paradigms.

In the Go/NoGo paradigm, the subject is required to perform speeded responses on Go trials (e.g., pressing a button in response to the letters A, Y, L, P) and to inhibit responding on presentation of the letter X (a NoGo trial). By having many more Go than NoGo trials, responding rather than inhibiting is made prepotent. The index of inhibitory control (i.e., inhibition of a prepotent response) is the number of mistaken responses (commission errors) a subject makes on NoGo trials. By contrast, the Stop-signal paradigm indexes the inhibition of an ongoing (already started) response. The task is similar but for the fact that a delay is inserted between the imperative stimulus (one of the Go stimuli) and the Stop-signal stimulus (e.g., conversion to the letter X). The index of inhibitory control is now the duration of the stopping process. This measure, known as the stop-signal reaction time (SSRT), is estimated from a model that makes use of the number of failed and successful inhibitions along with assumptions about Stop and Go processes (see Logan 1994, for review). A particularly good way of estimating SSRT is to use a dynamic or "tracking" algorithm which sets Stop-signal delays for each subject on a trial-by-trial basis. It is important to note that SSRT has more dynamic range, is cognitively purer (see below), and is probably a more sensitive measure of response inhibition than commission errors on the Go/NoGo task.

Right Inferior Frontal Cortex Is Critical for Response Inhibition

Meta-analysis of block-designed and event-related neuroimaging studies in healthy adults supports a role for the prefrontal cortex, especially the right inferior frontal cortex (IFC), in response inhibition. In blocked-design studies (e.g., Konishi et al 1998, 1999; Menon et al 2001; Rubia et al 2001; Tamm et al 2002), blocks of Go trials are contrasted with blocks of mixed Go and NoGo trials, and the difference between these conditions is computed at each voxel. Although such contrasts do reveal the neural correlates of response inhibition, they also index differences associated with number of motor responses (unbalanced between the two blocks), increased task maintenance load (higher in Go/NoGo mixed than Go pure blocks), switching (required in Go/NoGo mixed blocks but not in Go pure blocks), and posterror processing. More precise are event-related designs (e.g., Bunge et al 2002; Durston et al 2002; Garavan et al 1999, 2002; Liddle et al 2001; Rubia et al 2003), which allow separate estimation of activation on Go and NoGo trials. This overcomes some of the confounds of blocked designs, but still it is the case that there are typically many more Go than NoGo trials, which is required to build up prepotent Go responding. It is thus possible that part of the contrast of Go with NoGo indexes the effect of an infrequent trial type (the "oddball effect"). This confound may be obviated by using the Stop-signal paradigm, in which the Stop signal delay can be set to result in failed and successful inhibitions in roughly equal proportions, which can then be contrasted directly (cf. Rubia et al 2003). It must also be noted that the comparison of failed and successful stops, as with blocked designs, is confounded with error detection processes that are likely evoked when the subject commits an error by not stopping.

Considered together and overlooking the potential confounds, these neuroimaging studies produce activations of widespread regions of frontal cortex (Figure 1). Particularly striking is

the predominance of right-hemisphere activation, especially within the inferior frontal (ventrolateral) region. That the right IFC is specifically necessary for response inhibition is strongly suggested by a lesion study of patients with frontal lobe damage (Aron et al 2003b). Nineteen patients with unilateral right frontal damage were compared with 17 patients with unilateral left frontal damage and 20 healthy control subjects using a tracking version of the Stop-signal task. Using structural magnetic resonance imaging (MRI) methods, damage to each hemisphere was estimated within five sectors: the superior, middle, inferior, and orbital frontal gyri, as well as a medial area encompassing the anterior cingulate and supplementary motor area. First, it was found that right frontal patients had significantly slower SSRT than left frontal patients (while left frontal patients were no different from control subjects). In addition, the amount of damage to the right IFC (and no other region of right or left PFC) was shown to be significantly correlated with SSRT: those patients with the greatest damage to this region had the slowest SSRT. This result complements the imaging meta-analysis by demonstrating that the right IFC is necessary for response inhibition.

Response Inhibition Deficits in ADHD May Be Associated with Functional Activation Change and Volumetric Reduction of Right IFC

Numerous studies have documented behavioral response inhibition deficits on Go/NoGo tasks in child and adult ADHD (e.g., Casey et al 1997; Durston et al 2003; Slaats-Willemse et al 2003; Vaidya et al 1998), and there are more than 20 reports of slowed SSRT (see for review/meta-analysis: Lijffijt et al, in press; Nigg 2001; Oosterlaan et al 1998). While it is the case that ADHD patients in some of those studies often also showed significantly increased response speed (see meta-analysis by Oosterlaan et al 1998) and significantly increased response speed variability (e.g., Bedard et al 2003; Scheres et al 2001), some of the studies have clearly shown significant SSRT slowing even when controlling for response speed (or in the absence of increased response speed on Go trials) (Aron et al 2003a; Bekker et al 2004; Murphy 2002; Overtoom et al 2002). A meta-analysis of stop tasks in child and adult ADHD also confirms a disproportionate elongation of SSRT relative to Go reaction time (RT) (Lijffijt et al, in press).

Although decrements in response inhibition performance may have multiple sources, the findings in healthy adults (reviewed in the previous section) strongly implicate the integrity of right IFC for intact performance. Interestingly, a growing body of ADHD research indicates both structural and functional deficits in the right IFC.

In structural imaging, there have been about 30 studies comparing children or adolescents with ADHD to control groups (see chapter by Seidman [2005] and review by Giedd et al 2001). The emerging picture is that individuals with ADHD exhibit smaller total cerebral volume and smaller PFC, with these effects greater in the right hemisphere. In addition, there appear to be changes to the corpus callosum, caudate, pallidum, and cerebellum. A recent report, using automated cortical analysis techniques, found the greatest morphological reductions in right IFC for child and adolescent ADHD patients compared with matched control subjects (Sowell et al 2003). Another report found significant reductions in right IFC in ADHD children and their unaffected siblings (Durston et al 2004). An earlier study found that the volume of right frontal cortex correlated with response inhibition behavioral measures in ADHD children (Casey et al 1997).

Several functional imaging studies have studied response inhibition in ADHD compared with control subjects with somewhat conflicting results. In a study by Vaidya et al (1998), children performed two Go/NoGo tasks with and without methylphenidate (MPH). Relative to control subjects, ADHD children off drug made more NoGo errors on both tasks and had greater activation in inferior, middle, superior, and other frontal regions of interest on one task. In a study by Rubia et al (1999), adolescents with ADHD had marginally impaired response inhibition compared with control subjects and significantly reduced activity, specifically within the right IFC. In a study by Durston et al (2003), children with ADHD made significantly more errors on NoGo trials and showed significantly increased activation of right superior and middle frontal gyrus. A recent functional magnetic resonance imaging (fMRI) study examining fragile X retardation sufferers (who are also often diagnosed with ADHD) found that the degree of expression of fragile X mental retardation protein (involved in brain development) correlates with functional activation in right IFC and striatum associated with response inhibition (Menon et al 2004). Although these imaging studies are inconsistent with respect to the direction of differences in fMRI signal in ADHD compared with control subjects, they do consistently point to right-lateralized differences in the frontal cortex. Complementary to these results, electroencephalogram (EEG) event-related potential studies have found a significant attenuation of the N2 wave (the NoGo potential postulated to be a signature of behavioral inhibition) in ADHD children relative to control subjects, with the difference localized to the right IFC (Pliszka et al 2000; Smith et al 2004). Another study (discussed below in more detail) found that medicated ADHD children with a particular dopamine allele showed a change in theta activity (indicating increased arousal) over right frontal cortex during a continuous performance task with a response inhibition component (Loo et al 2003).

Further evidence for the relation between right IFC integrity and response inhibition comes from studies of normal development. Many such studies, too numerous to review here, have shown that children have impaired response inhibition relative to adults (e.g., van den Wildenberg and van der Molen 2004). A functional neuroimaging study showed significantly less right IFC activation for children compared with adults for response inhibition (Bunge et al 2002). A structural imaging comparison of adolescents and adults showed significantly smaller volumes in bilateral caudate and right IFC (Sowell et al 1999). As adults with ADHD have a behavioral profile of significantly poorer response inhibition than matched control subjects (Aron et al 2003a; Murphy 2002; Ossmann and Mulligan 2003), it is plausible that this, too, owes to functional change of right IFC. This predicts that structural studies comparing ADHD adults with matched control subjects should find morphologic change in the right IFC.

In summary, there exists considerable evidence to support the hypothesis that response inhibition deficits in ADHD are related to functional and volumetric changes to the right IFC.

Role of the Striatum in Response Inhibition and ADHD

As indicated above, a number of functional neuroimaging studies of ADHD and fragile X syndrome have also implicated the striatum in response inhibition (e.g., Casey et al 1997; Menon et al 2004; Rubia et al 1999; Vaidya et al 1998), and findings of striatal pathology in structural imaging of ADHD are fairly consistent (see Seidman [2005] and review by Giedd et al 2001). However, in healthy subjects, evidence for basal ganglia involve-

ment in response inhibition is mixed. Meta-analysis of neuroimaging studies of Go/NoGo and Stop-signal tasks in healthy adults–see Figure 1–shows that only 2 out of these 11 studies reported caudate or putamen activation (also see a recent study by Kelly et al 2004). It could be that such activations are seldom reported because most studies have restricted their interpretations to the frontal cortex for which there is a clear hypothesis, rather than using strict whole-brain corrections for multiple tests and then interpreting all surviving activations. However, it is noteworthy that most of these studies did nevertheless report whole-brain results, suggesting that basal ganglia activation was not present at the same threshold as prefrontal activation.

Other evidence comes from neuropsychology and lesion work. Patients with Parkinson disease had significantly slower SSRTs (Gauggel et al 2004), as did patients with nonspecific lesions of the basal ganglia owing to cerebrovascular events or tumor resections (Rieger et al 2003). In rats, lesions of the medial striatum (probably corresponding to the caudate in humans) led to estimates of significantly increased SSRT, although the underlying cause for this may have had more to do with changes in response control than with the speed of inhibition itself (Eagle and Robbins 2003).

In summary, while there is clear evidence for pathology of striatum and abnormal activation change during response inhibition in ADHD, it is not entirely clear if the striatum is necessary for NoGo and Stop-signal tasks. Future research is required to clarify whether the underlying network is truly frontostriatal and whether this network rather than the right IFC alone should serve as a phenotype.

Heritability of Response Inhibition and Single-Gene Association Studies in ADHD

A crucial criterion for response inhibition to count as an endophenotype is that behavioral performance (or functional activation/EEG correlates) are shown to be heritable. To date, the evidence for this is partial but suggestive. In a study of ADHD probands with a family history of ADHD, their nonaffected siblings, and normal control subjects, Slaats-Willemse et al (2003) showed that the nonaffected siblings had response inhibition deficits (with measures intermediate between control subjects and the ADHD siblings). In a study of ADHD children, Crosbie and Schachar (2001) found that the group with poor inhibition was associated with a significant increase in the prevalence of ADHD in their families than those with good inhibition. While both of these studies support response inhibition as a cognitive endophenotype, neither was capable of separating out shared environmental factors. By contrast, a study of 237 preschool healthy twin pairs found that response time on Go trials (and a teacher's rating of attention) could be attributed to shared genes and nonshared environmental influences, although it was unclear whether commission errors on that task could be similarly explained (Groot et al 2004). Although speeded responding on Go trials is sometimes interpreted as impulsivity, it is not clear that this relates to response inhibition per se. A recent study also examined healthy twin pairs performing a Go/NoGo task with event related potential (ERP) monitoring (Anokhin et al 2004). Approximately 60% of the variance in NoGo N2 and P3 amplitudes (EEG components indexing frontal lobe processing) was attributed to genetic factors.

In a specific analysis of a single gene, ADHD children with a 7-repeat allele for the DRD4 gene (a putative ADHD marker) had significantly faster RTs on Go trials (and showed higher frequency and intensity of body activity levels) relative to ADHD children without the 7-repeat allele (although see Swanson et al 2000 for evidence suggesting the 7-repeat allele is not associated with neuropsychological deficits). Another study examined dopamine transporter (DAT1) 10-repeat versus DAT1 9-repeat allele status in ADHD children using EEG and a continuous performance test (with a response inhibition measure) (Loo et al 2003). Children in the 10-repeat group made significantly more commission errors and responded differently to methylphendiate as measured by EEG, showing a reduction of theta activity (increased arousal) specific to the right frontal cortex.

The importance of response inhibition/right PFC as a potential endophenotype is underscored by the finding of Menon et al (2004) that the degree of expression of fragile X mental retardation protein (involved in brain development) correlated with blood oxygenation level dependent (BOLD) measures from right IFC (as well a striatum). It is also interesting to note that right IFC structure correlates (negatively) with CAG repeat length of the Huntington's gene so that those patients likely to develop the disease sooner (longer repeat length) have smaller volumes (Kassubek et al 2004; Thieben et al 2002) that right IFC is a brain region showing maximal asymmetry in the frontal cortex (Watkins et al 2001), and that this region is one of the last to develop in ontogeny and phylogeny (Pandya and Barnes 1987). Such findings suggest that this brain region is particularly sensitive to genetic control. While a multitude of studies have reported associations between genetic polymorphisms and ADHD (especially for dopamine and noradrenaline-related genes such as DAT1, DRD4, dopamine-beta-hydroxylase, and 5-HT_{1B}), we are not aware of associations between ADHD and genes for cortical patterning or synaptogenesis. Nevertheless, linkage studies have recently revealed multiple chromosomal loci harboring potential susceptibility genes (Ogdie et al 2004).

Together these studies strongly motivate further direct investigation of heritability and single-gene association of response inhibition, as well as investigation of other, finer, measures such as vigilance/sustained attention (which we discuss in the following section).

Neuromodulation, Response Inhibition, and the Right IFC

The importance of genes such as dopamine for ADHD, as well as the clinical efficacy of such drugs as methylphenidate, implicates the neuromodulatory systems in the disorder. Numerous studies have demonstrated that methylphenidate improves SSRT and NoGo indices in child and adult ADHD (e.g., Aron et al 2003a; Bedard et al 2003; Tannock et al 1995). However, MPH also has effects on the speed of Go responses, on Go response variability, and on discrimination errors on Go trials (e.g., Bedard et al 2003; Tannock et al 1995). Moreover, parametric increases in MPH dosage affect these variables in different and complex ways (cf. Bedard et al 2003; Konrad et al 2004). Such complexity is not surprising given that 1) MPH affects the noradrenergic (NA) (see Arnsten 2005), dopaminergic (DA) (see Volkow 2005), and serotonergic (5-HT) systems; 2) these neurotransmitter systems are highly interactive (see Arnsten et al 1996); and 3) both DA (Grace 1991) and NA (Aston-Jones et al 1999) have tonic and phasic modes that can be identified with different aspects of cognitive function. For example, tonic and phasic modes of DA may play different roles in the stability versus plasticity of cortical activation states, thus differentially affecting maintenance versus updating of working memory (Bilder et al 2004). The relative

balance of tonic versus phasic DA (potentially under genetic control) (Bilder et al 2004) could also be germane in the context of response inhibition, for example, by influencing the degree to which a response is prepotent. Therefore, the clinical and neuropsychological efficacy of MPH may derive from effects on multiple cognitive functions. Below, we show that some of these functions are fairly well understood and can be related to response inhibition tasks as well as to the right IFC.

Neuroimaging and lesion studies have shown that the right IFC participates in a network sensitive to the detection of low-frequency, unpredictable events requiring attention (see for review Corbetta and Shulman 2002). It is possible that part of the signal in the inferior frontal region depends on noradrenergic modulation from the brainstem locus coeruleus (LC). The LC receives input (in particular) from the lateral PFC (Arnsten and Goldman-Rakic 1984), fires more to behaviorally relevant stimuli (targets) than to irrelevant distractors, and is needed especially during attentional tasks that are made difficult by temporal unpredictability or distractor interference (see for review Aston-Jones et al 1999). The PFC, in turn, receives noradrenergic input in response to sudden changes in task demands (Dalley et al 2001).

Although this pattern of results mainly concerns vigilance tasks in monkeys and tests of spatial and temporal orienting of attention in humans, it is plausible that there are underlying functions in common with Stop-signal and NoGo response inhibition. In particular, it is clear that these tasks also entail stimulus-driven ('target') attention, unpredictability, and vigilance (or "sustained attention"). Such considerations lead to the prediction that drugs that alter noradrenergic tone should affect response inhibition. In fact, it has already been shown that the noradrenergic antagonist yohimbine disrupted NoGo (and not Go) trials in monkeys (Ma et al 2003) and that the noradrenaline reuptake inhibitor, desipramine, speeds SSRT in children with ADHD (Overtoom et al 2003). Moreover, another selective noradrenaline reuptake inhibitor, atomoxetine, has clinical efficacy in ADHD (Michelson et al 2003). Given the role of the NA system in attention, perhaps partly mediated by an LC/right IFC circuit, and the importance of right IFC pathology for ADHD, this system should be investigated with respect to component functions such as vigilance and stimulus-driven attention, which are constituents of response inhibition tasks.

There may be other component functions related to the DA and 5-HT systems. It has been shown, for example, that nicotine (administered in patch form) speeds SSRT in adolescents with ADHD (Potter and Newhouse 2004). In addition to its effects on cholinergic systems, this mode of administration of nicotine could lead to slow release and increasing tonic levels of DA, rather than effects on the phasic DA system. Increases in tonic DA may serve to enhance maintenance of task rules or goals (Bilder et al 2004), rather than having any effect on attention per se. The dorsolateral PFC, especially left-lateralized, has been associated with representation of task rules (e.g., "press the left key for a leftward going arrow and the right key for a rightward going arrow, but do nothing if there is a beep") (see discussion in Aron et al 2004a; Garavan et al 2002). The serotonergic system is also implicated in response inhibition (see Overtoom et al 2003 for discussion in relation to ADHD), as well as in impulse control (for example, in relation to the capacity of rats to inhibit responding during an anticipatory period for an RT task, e.g., Dalley et al 2002).

In summary, multiple component functions may contribute to the speed with which a subject cancels a planned/prepotent response (Figure 2). Such functions may include: 1) maintaining and successfully executing the task rules; (2) maintaining alertness/vigilance for the unpredictable occurrence of the Stop-signal; 3) processing the Stop-signal, which requires detecting it as the target for a different action/nonaction and which may require shifting attention from the visual to the auditory domain (although most neuroimaging studies present both Go stimuli and Stop-signal stimuli within the visual domain); and 4) the inhibition itself, which constitutes the executive control and which may require suppression, at the neural-systems level, by PFC of the motor system (cf. Aron et al 2004b). Different functions such as these may be related to different neurotransmitter systems or to different modes (i.e., tonic vs. phasic) of those systems. Right IFC pathology could affect the capacity to maintain alertness, perhaps by reducing efferent input to the LC, or the reverse could be the case: LC input to right IFC could be rendered less effective. Right IFC pathology could also affect the detection of the Stop-signal, the shifting of attention from visual to auditory domains (or cross-modal integration).

Indeed, ADHD researchers have recently begun to take such a componential approach to response inhibition performance by exploring parametric increases in stopping difficulty (Durston et al 2003); selective stopping (Bedard et al 2003); the effects on stopping of different drug treatments (Overtoom et al 2003); the time-course of sensory, attentional, and control processes (Smith et al 2004); and the differential affects of MPH on sustained attention and other components of executive function (Konrad et al 2004). Such an approach could help characterize better the functional role of the IFC, as well as providing "purer" measures, which are more likely to yield association with genes by virtue of requiring more discrete neural systems.

Conclusion

Response inhibition, as measured by Go/NoGo and Stop-signal tasks, has emerged as one of the principal paradigms for studying ADHD. It has also been heavily explored in neuroimaging, lesion, neurophysiological, and electrophysiological studies in humans, nonhuman primates, and rats. Although response inhibition is only one out of several cognitive functions that have 1) consistently distinguished ADHD patients from control subjects and 2) shown some evidence of heritability, it stands out with respect to the neuroscientific evidence. The specificity of the implicated brain regions in healthy adults, as well as observations of functional and structural change to those regions in ADHD, argues in favor of response inhibition (and its component functions) as cognitive endophenotypes.

Meta-analysis of functional neuroimaging in healthy adults indicates that widespread regions of frontal cortex (and in a few studies, striatum) are activated by the requirement to inhibit a prepotent response (Figure 1). In particular, there is a predominance of right hemisphere frontal activation, especially in the inferior frontal (or ventrolateral) region. Lesion studies in humans confirm that the right IFC is necessary for response inhibition, because those patients with the greatest damage to that region had the greatest response inhibition deficits. It is well established that children and adults with ADHD have response inhibition deficits, for example, elongated SSRT on the Stop-signal task (and that such slowing is often disproportionately greater than Go RT slowing). Structural neuroimaging in ADHD has fairly consistently pointed to gray matter density reductions in striatum and right IFC (in particular), and one study showed this was also the case for nonaffected siblings of ADHD children

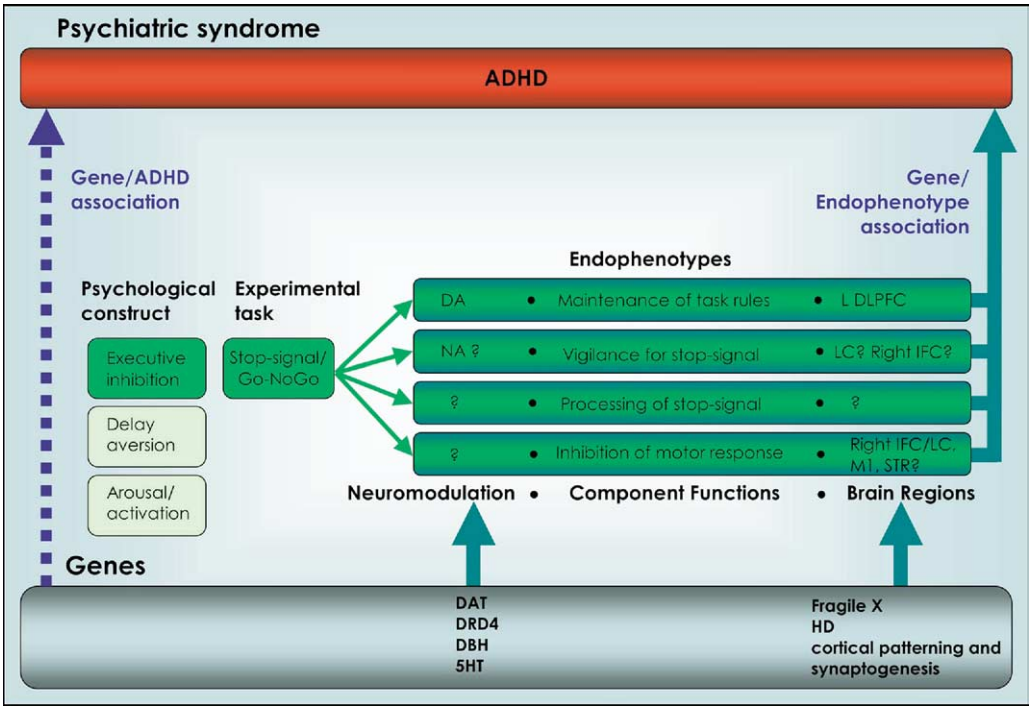

Figure 2. Multiple components of response inhibition paradigms may stand as endophenotypes intermediate between ADHD symptomatology and genes. Instead of the simple gene/ADHD association (dotted vertical line on left of figure), gene/endophenotype associations can be investigated (solid vertical line on right). Endophenotypes can consist in: 1) psychological constructs such as "executive inhibition," "delay aversion," etc., 2) the dependent measures for the task at hand, e.g., stop-signal reaction time (SSRT) or Go versus NoGo activations in imaging contrasts, and 3) cognitive components of the Stop-signal paradigm, such as vigilance, Stop-signal processing, and the inhibition itself. Accumulating evidence suggests such cognitive components may relate to distinct brain regions, such as dorsolateral PFC, right inferior frontal cortex (IFC), motor cortex (M1), striatum (STR), and locus coeruleus (LC), as well as neurotransmitter systems (such as dopamine [DA], noradrenaline [NA], and serotonin [5-HT]). These neurotransmitter systems can, in turn, be related genes such as those for dopamine (DAT, DRD4), noradrenaline (DBH), and serotonin (5-HT_{1A}). Other genes may relate specifically to development/pathology of brain regions, such as the Huntington's disease (HD) gene and genes for Fragile X syndrome. In addition, but not shown, are environmental factors and environment-gene interactions. ADHD, attention-deficit/hyperactivity disorder; PFC, prefrontal cortex.

(Durston et al 2004). Functional neuroimaging of children and adolescents with ADHD and adults with fragile X syndrome finds significant changes in right IFC, as well as striatum, associated with response inhibition. Although these studies are inconsistent with respect to whether increases or decreases were seen relative to control subjects, the consistency of the right IFC findings is striking.

The fragile X study, in particular, underscores the importance of response inhibition/right IFC as a potential endophenotype, because there was a significant correlation between expression of fragile X mental retardation protein (involved in brain development) and BOLD measures from right IFC (as well as striatum). Other studies have found significant correlations between CAG repeat length of the HD gene and right IFC volume. As the right IFC shows maximum asymmetry in the frontal cortex and develops last in ontogeny and phylogeny, it could be a brain region that is particularly sensitive to genetic control. Future studies may better characterize other genes for synaptogenesis and cortical patterning for this region.

The role of neuromodulatory systems in ADHD is also clearly important. Perhaps the clearest avenue for future research concerns the convergence between right IFC and the noradrenaline system and how this may subserve vigilance and/or other functions underlying response inhibition. Future studies in humans might extend intriguing recent results in nonhuman primates which relate NA manipulations to response inhibition performance and imaging measures (Avery et al 2000; Ma et al 2003) and to explore in more detail which behavioral components may be associated with genes for NA metabolism (such as dopamine-beta-hydroxylase, which has recently been associated with ADHD in multiple studies).

Although our own data have shown that SSRT is related to the integrity of the right IFC, we believe that further work is required to better characterize which underlying cognitive components are truly affected. Response inhibition, measured either by SSRT or number of commission errors, could comprise such components as maintaining task rules, maintaining alertness/vigilance for the unpredictable occurrence of the Stop-signal, processing the Stop-signal (including detection and cross-modal integration), and the inhibition itself. In this sense, the simple act of inhibiting a prepotent response has features consistent with several of the principal theoretical perspectives of ADHD (i.e., "executive function," "working memory," "temporal/delay processing," and "activation/arousal") (Castellanos and Tannock 2002). It is unlikely that one of these is primary; instead, different components may be affected differently in different people, so that ADHD is more a continuum than a category (Levy et al 1997) and reflects the interaction of multiple genes and neural systems.

Nevertheless, the evidence summarized here suggests that response inhibition is a promising means of tapping such systems. It could be that association and heritability studies may better proceed by using a combined phenotype comprising right IFC structure/function/response inhibition. Meanwhile, other approaches might be directed toward substantiating the role of

the striatum in response inhibition and conducting psychopharmacological and neuroimaging studies targeted at putative components of response inhibition. Ultimately, the virtue of such approaches is to develop a fine-grained cognitive psychology of response inhibition. The cognitive components, so revealed, will be better rooted in known neural systems and so can be better related to the neuromodulatory genes already associated with ADHD, as well as genes for brain development.

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