The Molecular Genetics of Executive Function: Role of Monoamine System Genes

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Executive control processes, such as sustained attention, response inhibition, and error monitoring, allow humans to guide behavior in appropriate, flexible, and adaptive ways. The consequences of executive dysfunction for humans can be dramatic, as exemplified by the large range of both neurologic and neuropsychiatric disorders in which such deficits negatively affect outcome and quality of life. Much evidence suggests that many clinical disorders marked by executive deficits are highly heritable and that individual differences in quantitative measures of executive function are strongly driven by genetic differences. Accordingly, intense research effort has recently been directed toward mapping the genetic architecture of executive control processes in both clinical (e.g., attention-deficit/hyperactivity disorder) and nonclinical populations. Here we review the extant literature on the molecular genetic correlates of three exemplar but dissociable executive functions: sustained attention, response inhibition, and error processing. Our review focuses on monoaminergic gene variants given the strong body of evidence from cognitive neuroscience and pharmacology implicating dopamine, noradrenaline, and serotonin as neuromodulators of executive function. Associations between DNA variants of the dopamine beta hydroxylase gene and measures of sustained attention accord well with cognitive-neuroanatomical models of sustained attention. Equally, functional variants of the dopamine D2 receptor gene are reliably associated with performance monitoring, error processing, and reinforcement learning. Emerging evidence suggests that variants of the dopamine transporter gene (DAT1) and dopamine D4 receptor gene (DRD4) show promise for explaining significant variance in individual differences in both behavioral and neural measures of inhibitory control.

Key Words: Attention, dopamine, executive function, genetics, noradrenaline, serotonin

How genetic variation gives rise to individual differences in cognitive ability is a central question for science. Executive function is an umbrella term used to describe a constellation of cognitive processes, including sustained attention, response inhibition, working memory and error processing, which allow humans to guide behavior in a goal-directed and adaptive fashion (1). The frontal lobes have long been identified as the critical hub for executive control processes, coordinating complex behavior through their extensive reciprocal cortical and subcortical connections; this seems reasonable, because patients with lesions to the frontal lobes (2) and psychiatric disorders of putatively frontal origin, such as schizophrenia and attention-deficit/hyperactivity disorder (ADHD), all display impairments of executive control (3–5). Findings from behavioral genetics using twin designs indicate that aspects of executive function are highly heritable (6). This is not surprising given that the morphology of the frontal lobe and its connecting structures appears to be under tight genetic regulation (7).

To determine how DNA variation gives rise to individual differences in executive ability, researchers typically employ the method of allelic association (8–11). In addition to investigating associations between a candidate gene and disorders, allelic association can also be used to investigate how allelic variation in a polymorphism, such as a single nucleotide polymorphism of a particular gene, associates with measures of cognitive ability. Central to the candidate gene approach is the assumption that genes of interest can be identified, a priori, on the basis of knowledge of the biological substrates of the phenotype in question. The hypothesis-driven candidate gene approach is distinct from the hypothesis-free genome-wide association study (GWAS) approach. The latter can be powerful for gene mapping when there is limited evidence from neuroscience to guide the selection of candidate genes. Although promising GWAS leads (12) for memory-related phenotypes have been identified (but see Need *et al.* for nonreplication) (13), to date there are no published studies that attain the accepted significance level of $p = 5 \times 10^{-08}$ for genome-wide association for executive phenotypes. It should also be noted that there remains considerable controversy regarding the ability of a GWAS versus candidate-gene approach to identify genes for complex phenotypes (14). This review focuses on current knowledge of the molecular genetics of executive function that has been derived from candidate gene studies. We draw on findings from nonclinical populations as well as evidence from clinical disorders, such as ADHD, in which the association between gene variants and executive phenotypes has been investigated.

A candidate-gene approach can prove powerful in elucidating the underlying genetics of cognition when there is a robust scientific model to guide predictions (8–11). For example, the selection of candidate genes for executive processes can be informed by our knowledge of their biological substrates, including their cognitive-neuroanatomy and neurochemistry (Figure 1). Knowledge from cognitive neuroscience can thereby generate hypotheses regarding the relationship between a gene and a cognitive process, and can minimize the potential for false positive associations. Here we capitalize on current knowledge from cognitive neuroscience and psychopharmacology to review the extant literature on the molecular genetic correlates of three exemplar executive processes: sustained attention, response inhibition, and error processing. Table 1 summarizes the molecular genetic correlates of these phenotypes, including wherever possible, information from functional genomics regarding the molecular impact of associated gene variants.

Cognitive Neuroscience and Pharmacology of Sustained Attention

Contemporary cognitive neuroscience defines sustained attention as the ability to maintain goal-directed focus in the absence of exogenous or external cues (15). Although sustained attention was

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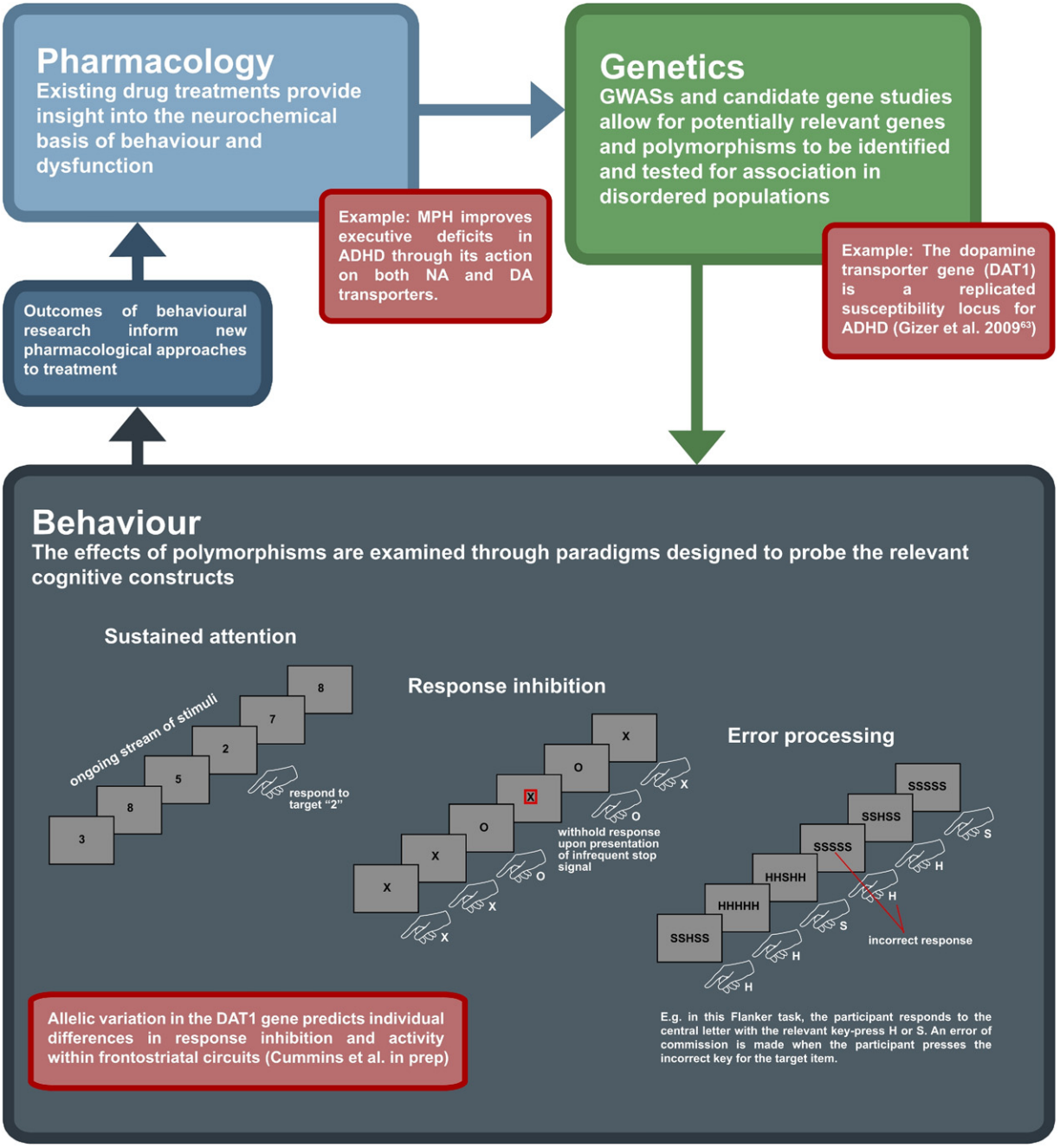

Figure 1. The candidate gene approach to studying the genetics of executive control. Reliable behavioral and neural probes of executive function such as sustained attention, response inhibition, and error processing can be interrogated at a genetic level. Knowledge from cognitive neuroscience and pharmacology allows a priori identification of molecular targets of relevance to cognition. Allelic variation within DNA variants or polymorphisms coding for those molecular targets can then be tested for association with the cognitive trait of interest. Insights into the molecular genetic architecture of cognitive abilities can then provide a basis for further pharmacologic research, particularly if the functional outcomes of genetic polymorphisms are known and drugs can be used to target this functional change at the molecular level. ADHD, attention-deficit/hyperactivity disorder; DA, dopamine; GWAS, genome-wide association study; MPH, methylphenidate; NA, noradrenaline.

traditionally studied using cognitive tasks that required continuous monitoring of stimulus streams for many tens of minutes (Figure 1), there is now considerable evidence that attention fluctuates over time periods as short as 1 sec (16,17). Thus, current accounts of sustained attention emphasize both the gradual drifts in performance with time that may result from diminished arousal but also the moment-to-moment fluctuations in top-down attentional control.

Convergent evidence from human lesion and functional neuroimaging supports the view that sustained attention is achieved through the reciprocal interaction between cortical and subcortical areas. Specifically, the right inferior frontal gyrus, anterior cingulate, and inferior parietal lobe act via thalamic nuclei to exert top-down (endogenous) control over brainstem-activating structures, such as the locus coeruleus which promotes the release of noradrenaline to the cortex (18–23). Within this network, the cortical nodes, such as

Table 1. A Summary of the Associations Between Genetic Variants and Behavioral or Physiological Outcomes

Neurotransmitter System Affected	Genetic Variant	Molecular Outcome	Cognitive Paradigm	Behavioral/Physiological Association
		Executive Function: Sustained Attention		
Noradrenaline	-1021 C/T SNP in DBH gene (59)	T allele associated with ↓ DβH activity, ↓ DA-to-NA conversion (57)	Continuous performance task	Children with ADHD with CC homozygosity showed impaired performance (more commission and omission errors).
Noradrenaline	-1,021 C/T SNP in DBH gene (63)	T allele associated with ↓ DβH activity, ↓ DA-to-NA conversion (57)	Sustained attention to response task	T allele associated with poorer performance (more commission errors) in nonclinical individuals.
Dopamine, noradrenaline	TaqI polymorphism of DBH gene (61)	T allele associated with ↓ DβH activity (54)	Temporal order judgment task	ADHD individuals with A2/T-allele homozygosity showed impaired performance.
Dopamine	VNTR in 3′-untranslated region of DAT1 gene (65)	In vitro evidence of 10-repeat allele and ↑ expression (188)	Continuous performance task	Children with ADHD and homozygous for 10-repeat allele showed impaired performance compared with heterozygotes or homozygotes for the 9-repeat allele.
Dopamine, possibly noradrenaline	VNTR in exon 3 of DRD4 gene (69)	↓ Ability of DA to inhibit camp formation associated with 7-repeat suggesting ↓ functional activity (189)	Sustained attention to response task	ADHD children with at least one 7-repeat allele performed better than those without.
Dopamine, possibly noradrenaline	VNTR in exon 3 of DRD4 gene (70)	See above	Sustained attention to response task	ADHD children without 7-repeat allele made more omission errors than ADHD children with the 7-repeat allele or control children with or without the 7-repeat allele.
Dopamine, possibly noradrenaline	VNTR in exon 3 of DRD4 gene (71)	See above	Continuous performance task	Children and adolescents with ADHD and with at least one 7-repeat allele made more commission errors; those homozygous for the 4-repeat allele made fewer omission or commission errors.
Dopamine	Rs 2,075,654 and rs1079596 SNPs of DRD2 gene (74)	Unknown	Conners' continuous performance task	SNPs significantly associated with greater commission error rates in a cohort including children with ADHD, their affected and unaffected siblings, and their parents.
Dopamine	TaqIA polymorphism of DRD2 gene (75)	A1 allele associated with reduced D2 receptor density in striatum and caudate (178–180)	Continuous performance task	Alcoholic men with at least one TaqIA1 allele showed a greater number of omission errors.
Serotonin	5-HTTLPR polymorphism in transcriptional control region of 5-HTT gene (76)	Long allele associated with ↑ 5-HTT mRNA and ↑ 5-HT uptake compared with short allele (77)	Continuous performance task	Individuals with schizophrenia and homozygotic for the long allele had higher rates of omission and commission errors compared with carriers of the short allele.
Serotonin	T/C SNP at codon 102 for 5-HT_{2A} gene (79)	↓ Expression of C allele may result in deficit of 5-HT_{2A} receptor expression (78)	Continuous performance task	T allele associated with lower hit rate and more commission errors in individuals with schizophrenia compared with C allele.
		Executive Function: Response Inhibition		
Dopamine, possibly noradrenaline	VNTR in Exon 3 of DRD4 gene (119)	See above	Go/NoGo task	Nonclinical individuals with the 4-repeat allele showed less accurate performance on tasks containing 72% go trials (the more demanding condition) compared with 50% go trials (less demanding), whereas individuals with the 7-repeat allele did not perform differently in the 72% go condition compared with the 50% go condition.
Dopamine, possibly noradrenaline	VNTR in exon 3 of DRD4 (66)	See above	Matching familiar figures (measure of impulse control), Go/NoGo task, stop task	ADHD children with 7-repeat allele made more errors on matching familiar figures task than those without the allele; 7-present and 7-absent groups did not differ on RT or % inhibitions on Go/NoGo task or % inhibitions on the stop task.

Table 1. (continued)

Neurotransmitter System Affected	Genetic Variant	Molecular Outcome	Cognitive Paradigm	Behavioral/Physiological Association
Dopamine, possibly noradrenaline	VNTR in exon 3 of DRD4 (69)	See above	Sustained attention to response task (with response inhibition component)	ADHD children without 7-repeat allele made more commission and omission errors compared with those with 7-repeat allele.
Dopamine, possibly noradrenaline	VNTR in exon 3 of DRD4 (120)	See above	Stop-signal task	Nonclinical adults with the 7-repeat allele displayed impaired inhibition.
Dopamine	VNTR in 3′-untranslated region of DAT1 gene (121)	See above	Opposite world task (from Test of Everyday Attention for Children, TEA-ch)	boys scoring high on a teacher-rated report of ADHD symptoms and who were homozygous for the 10-repeat allele displayed poorer response inhibition.
Dopamine	VNTR in 3′-untranslated region of DAT1 gene (122)	See above	Go/NoGo task	Youth with ADHD and homozygous for the 10-repeat allele showed ↑ inhibition-related activation during fMRI than those who were carriers of the 9-repeat allele.
Dopamine	VNTR in 3′-untranslated region of DAT1 gene (123)	See above	Stop-signal task	Adults carrying the 9-repeat allele showed greater inhibition-related activation during fMRI than 10-repeat homozygotes.
Dopamine	SNP of COMT gene (val/met substitution) (123)	Met allele has ↓ enzyme activity compared with val allele (190), so decreased DA in the synapse.	Stop-signal task	Adults aged 18–30 and carrying at least one met allele showed greater inhibition-related activation during fMRI than those with the val/val genotype.
Dopamine	Rs37020 of DAT1 gene (Cummins *et al.*, in preparation)	Unknown	Stop-signal task	Allelic variation associated with stop-signal reaction time (SSRT) and task-related activation in prefrontal and striatal (caudate) regions during fMRI.
Noradrenaline, serotonin, dopamine	VNTR in promoter region of MAO-A gene (125)	Number of repeats influences protein transcription and enzymatic activity (191)	Go/NoGo task	Nonclinical males with the high-activity allele showed ↑ activation in the rPFC during fMRI whereas those with the low-activity allele showed greater activity in the right superior parietal cortex and bilateral extrastriate cortex.
Noradrenaline, serotonin, dopamine	VNTR in promoter region of MAO-A gene and 5-HTTLPR polymorphism in transcriptional control region of 5-HTT gene (127)	Long allele of 5-HTTLPR associated with ↑ 5-HTT mRNA expression and ↑ 5-HT uptake compared with short allele (77)	Go/NoGo task	Nonclinical males with the MAO-A high-activity allele and at least one 5-HTT short allele showed the greatest activation in anterior cingulate cortex (ACC) during fMRI. Participants homozygous for 5-HTT long allele and carrying MAO-A low-activity variant showed least activation. remaining participants intermediate
Serotonin	5-HTTLPR polymorphism in transcriptional control region of 5-HTT gene (128)	See above	Stop-signal task	Nonclinical individuals with at least one short allele were not more impulsive than those homozygous for the long allele.
Serotonin, dopamine, noradrenaline	SNP in intron 8 of TPH2 gene, VNTR in promoter region of MAO-A gene, G861C polymorphism of serotonin 1 B terminal autoreceptor gene (129)	Unknown	Stop-signal task	Nonclinical individuals homozygous for T allele of TPH2 SNP displayed ↑ SSRT. no association between other gene variants and task performance.
Serotonin	rs4570625 G/T and rs11178997 T/A SNPs of TPH2 gene (130)	Unknown	Continuous performance Go/NoGo task	Reduced NoGo anteriorization (anterior movement of P300 ERP during NoGo condition relative to go condition) in ADHD and control individuals with G/G rs4570625 genotype and T/T rs11178997 genotype.

Table 1. (continued)

Neurotransmitter System Affected	Genetic Variant	Molecular Outcome	Cognitive Paradigm	Behavioral/Physiological Association
		Executive Function: Error Processing		
Dopamine, possibly noradrenaline	SNP of COMT gene (val/met substitution) and -521 T/C SNP of DRD4 gene (174)	Met allele has ↓ enzyme activity compared with val allele (190), T allele of DRD4 SNP possibly associated with decreased transcriptional efficiency (175)	Flanker task	Nonclinical individuals with val/val COMT genotype displayed a larger error-related negativity (ERN) after stop errors than those with met/met genotype. Individuals homozygous for T allele of DRD4 SNP displayed larger ERN after choice errors and stop errors than those carrying the C allele.
Dopamine	TaqIA polymorphism of DRD2 gene (181)	See above	Probabilistic learning task	Healthy individuals carrying an A1 allele were poorer at learning to avoid actions with negative consequences. A1 carriers displayed less activation in posterior medial frontal cortex during fMRI.
Serotonin, dopamine	5-HTTLPR polymorphism in transcriptional control region of 5-HTT gene and TaqIA polymorphism of DRD2 gene (182)	As above	Probabilistic learning task	No association between ERN and DRD2 TaqI genotype in children. Children carrying the 5HTTLPR short allele or both the DRD2 TaqIA and the 5HTTLPR short allele had ↑ ERN.
Serotonin	5-HTTLPR polymorphism in transcriptional control region of 5-HTT gene (183)	As above	Flanker task	Nonclinical individuals homozygous for the short allele showed ↑ ERN amplitudes and trending towards ↑ Pe amplitudes compared with individuals homozygous for the long allele.
Serotonin	5-HTTLPR polymorphism in transcriptional control region of 5-HTT gene (184)	As above	Flanker task	Nonclinical individuals carrying the short allele showed impaired post-error and postconflict adjustments, ↑ error-related rostral ACC activation, and ↓ conflict-related dACC activation relative to individuals homozygotic for the long allele.
Serotonin	−1,019 C/G SNP in 5-HT_{1A} gene (185)	Reduced serotonergic neurotransmission (186)	Flanker task	Nonclinical individuals with CC genotype showed ↑ ERN and greater post-error slowing than GG or CG genotypes.

5-HT, serotonin; 5-HTT, serotonin transporter; ACC, anterior cingulate cortex; ADHD, attention-deficit/hyperactivity disorder; COMT, catechol-*O*-methyl transferase; DA, dopamine; DAT1, dopamine transporter 1; DBH, dopamine beta hydroxylase; DRD2: dopamine receptor D2; DRD4, dopamine receptor D4; ERN, error-related negativity; fMRI: functional magnetic resonance imaging; MAO-A, monoamine oxidase A; mRNA, messenger ribonucleic acid; NA, Noradrenaline; Pe, error positivity; rPFC, right prefrontal cortex; SNP, single nucleotide polymorphism; TPH, tryptophan hydroxylase; VNTR, variable number tandem repeat.

the inferior frontal gyrus and inferior parietal lobe are particularly important in maintaining attention on a moment-to-moment basis (17), whereas subcortical nodes, such as the thalamus, may be important for maintaining arousal over time (24).

The electrophysiology of sustained attention is possibly best characterized by changes in the frequency spectrum of oscillatory neural activity. A recent study reported increased activity in the alpha band over right inferior parietal regions up to 20 sec before an impending lapse of sustained attention, defined as a failed target detection (16). Activity in the alpha-band reflects cortical excitability suggesting that the increase in activity before a lapse represented a maladaptive disengagement of brain regions that are necessary for sustained attention (25).

The dominance of the right hemisphere for sustained attention, as found in human lesion, positron emission tomography, functional magnetic resonance imaging (MRI), and electroencephalogram (EEG) studies may be underpinned by the extensive innervation of the right frontal cortex by noradrenergic neurons arising from the locus coeruleus, a key modulator of arousal (26,27).

Pharmacologic manipulation of the noradrenergic system influences sustained attention in both animals and humans. The spontaneously hypertensive rat displays a deficit in sustained attention as measured by the five-choice serial reaction time task (5CSRT), a task that is considered analogous to the human continuous performance task (CPT; Figure 1). This deficit can be ameliorated by administration of the α2A adrenoceptor agonist, guanfacine (28). One study used the immunotoxin antidopamine-beta hydroxylase-saporin to lesion the noradrenergic projections to the prefrontal cortex (PFC) (29). These selective lesions impaired sustained attention performance on the 5CSRT, supporting the involvement of the locus coeruleus/noradrenergic system in sustained attention. Drugs that enhance both noradrenergic and dopaminergic signaling, such as L- and D-amphetamine also improve sustained attention deficit in spontaneously hypertensive rat (30).

In humans, experimental depletion of serotonin, dopamine and noradrenaline leads to deficits in sustained attention, as measured by accuracy and reaction time on a vigilance task, relative to a control condition (31). Although the depletion of multiple monoamines has clinical relevance because executive disorders involve multiple monoamine systems, this approach lacks specificity in terms of elucidating the primary neurochemical drivers of sustained attention.

Pharmacological challenge studies in both healthy and clinical populations support a critical role for noradrenaline in sustained attention. For example, reducing noradrenergic cell firing and release using low doses of the α2-adrenoreceptor agonist clonidine, impaired sustained attention in healthy volunteers (32). This effect was reversed by administration of idazoxan, a selective α2-adrenoreceptor antagonist in combination with an alerting noise burst designed to activate ascending arousal systems. Enhancing noradrenergic activity with the noradrenaline reuptake inhibitor atomoxetine also resulted in an improvement in sustained attention performance after 4–12 weeks of treatment in boys with ADHD (33).

Methylphenidate (MPH) is a stimulant medication commonly used to treat ADHD. Although the clinical benefit accrued from MPH is often attributed to blockade of the dopamine transporter (DAT), MPH is also a potent blocker of the noradrenaline transporter, thereby increasing noradrenaline concentrations in the PFC (34,35). MPH significantly improves sustained attention deficits in children (36) and adults (37) with ADHD. More direct evidence for the role of dopamine in sustained attention comes from rodent studies by Granon *et al.* in which either D1 antagonists (SCH23390) or agonists (SKF38393) were infused into rat medial PFC (mPFC) during the 5CSRT (38). Attentional performance was impaired after the D1 antagonist and rescued after the D1 agonist. Although the same study reports that the D2 antagonist sulpiride had no effect on performance, human research indicates that the D2 antagonist haloperidol causes significant impairments of sustained attention compared with placebo (39).

Serotonin is implicated in a range of psychiatric disorders that feature executive dysfunction, suggesting the possibility of serotonin involvement in sustained attention. Administration of serotonin reuptake inhibitors such as dosulepin (previously called dothiepin) and fluoxetine leads to impaired sustained attention in human studies (40). The more selective serotonin reuptake inhibitor escitalopram decreased functional MRI activity in areas related to sustained attention relative to placebo, although no behavioral outcome of this alteration was observed (41). In rats, infusion of the selective 5-HT_{1A} agonist 8-OH-DPAT (8-hydroxy-2-[di-*n*-propylamino]tetralin), into the mPFC improved target detection on the 5CSRT task in a dose-dependent manner, as did the selective 5-HT_{2A} antagonist M100907 (42). This suggests that the modulation of serotonergic transmission in the forebrain influences sustained attention.

The cholinergic system has also been implicated in attentional processes (43). Microdialysis reveals that rats performing the 5CSRT task have an increased efflux of acetylcholine in the cortex during the task (44) and 5CSRT performance is impaired in rats following a decrease in cortical acetylcholine efflux resulting from selective basal forebrain lesioning (45). The cholinergic system is further implicated in attention through its modulation by the serotonergic system (46–48), but the interaction between the cholinergic and serotonergic (and indeed the catecholaminergic) systems is demonstrably complex and beyond the scope of this review.

Genetics of Sustained Attention

Multiple lines of evidence suggest that individual differences in the ability to sustain attention might be explained by genetic differences. First, twin studies show robust additive genetic influences on measures of sustained attention in children (49). Sustained attention deficits also appear to show a familial risk profile, present in unaffected siblings of probands, in both schizophrenia (50) and ADHD (51).

As the foregoing section outlined, research examining cognitive neuroscience and pharmacology of sustained attention has allowed researchers to define a priori molecular targets for genetic analysis. Using this candidate gene approach, several studies have sought association between monoamine gene variants and sustained attention phenotypes in both clinical (e.g., ADHD) and nonclinical populations.

Noradrenaline Gene Polymorphisms and Sustained Attention

As reviewed above, dominant models from cognitive neuroscience highlight a strong neuromodulatory influence of noradrenaline on sustained attention. Not surprisingly, allelic variation in a number of genes of the noradrenergic system has been linked to sustained attention phenotypes. Dopamine beta hydroxylase (DβH) is the enzyme that catalyses the conversion of dopamine to noradrenaline within noradrenergic neurons and is coded for by the dopamine beta hydroxylase (DBH) gene (52). A number of functional polymorphisms of the DBH gene have been identified that may increase or decrease plasma DβH activity (53–57) and may lead to changes in noradrenaline excretion and blood pressure (58). The functional 1021 C/T single nucleotide polymorphism (SNP) in the 5′ flanking region of the gene has been shown to account for 35%–52% of plasma DβH activity, with the T allele being associated with

lower DβH activity and therefore a lower dopamine-to-noradrenaline conversion (57). Decreased DβH activity has been observed in children and adolescents with ADHD, and the functional 1021 C/T polymorphism of DBH has been associated with executive function and sustained attention in ADHD. In children with ADHD, Kieling and colleagues (59) used a combination of CPT and the Wisconsin Card Sorting Task. Participants homozygous for the C allele displayed diminished global executive function and had more errors of commission and omission on the CPT than participants carrying at least one T allele.

Another DBH polymorphism (rs2519152; TaqI) has been linked to both susceptibility for ADHD (60) and impairments in sustained attention (61). ADHD children with two copies of the A2 TaqI allele performed more poorly on the Sustained Attention to Response Task compared with ADHD children with only a single copy and to control children (61). Polymorphisms of the DBH gene have also been shown to influence sustained attention in nonclinical populations. Nonclinical individuals with more copies of the T allele of the 1021 C/T SNP demonstrated poorer performance on a sustained attention test, making more errors of commission than participants with more copies of the C allele (62). These data suggest that genes such as DBH might increase risk for disorders such as ADHD through their effect on the development of the neural systems for sustained attention.

Dopamine Gene Polymorphisms and Sustained Attention

As discussed earlier, the stimulant MPH is effective in the treatment of children with ADHD in approximately 60% of cases. Because MPH acts to inhibit the dopamine (and noradrenaline) transporter, the DAT1 gene has been pursued as a primary candidate gene for ADHD. Numerous studies have now confirmed that polymorphisms of the DAT1 gene, including the 10-repeat allele of a variable number of tandem repeat polymorphism (VNTR) within the 3′ untranslated region (3′-UTR) of the gene, confer a small amount of genetic susceptibility to ADHD (63).

Two studies in children with ADHD reported that individuals homozygous for the DAT1 10-repeat allele performed more poorly on a sustained attention task than individuals with other genotypes (64,65). The DRD4 gene, which encodes the dopamine D4 receptor, exhibits polymorphisms that could contribute to an underlying executive dysfunction in ADHD (66), such as SNPs in the promoter region of the gene (67) and a 7-repeat VNTR in Exon 3 (68). The relationship between this VNTR polymorphism and sustained attention remains unclear. In two studies, children with ADHD with the 7-repeat allele made fewer errors on a test of sustained attention than children without the allele (69,70). However, another study in ADHD children reported the opposite finding, with the 7-repeat allele associated with poorer performance on a CPT (71). The role of the 4-repeat allele of this VNTR is less established, although individuals homozygous for the 4-repeat allele demonstrated better performance (71). It should also be noted that because noradrenaline binds strongly to the D4 receptor (72), DRD4 gene polymorphisms could modulate activity of either dopaminergic or noradrenergic pathways.

Although allelic variation in the dopamine D2 receptor gene (DRD2) has been linked to psychiatric phenotypes including addiction and ADHD (73), only a limited number of studies have tested for association between variants of this gene and sustained attention phenotypes. One such study, involving a large cohort of ADHD individuals, their affected and unaffected siblings, and their parents, identified a significant association between performance on a CPT and SNPs rs2075654 and rs1079596 in the DRD2 gene, suggesting an influence of these SNPs over sustained attention (74). In male alcoholics, Rodríguez-Jiménez and colleagues (75) showed that individuals possessing the TaqIA1 allele of the ANNK1 gene, near the DRD2 gene, demonstrated poorer performance on a CPT than those without this allele.

Serotonin Gene Polymorphisms and Sustained Attention

Candidate gene studies have also found associations between ADHD phenotypes and the 5-HTT gene that encodes the serotonin transporter (63). Polymorphisms of the transcriptional control region of the 5-HTT gene have been shown to have an effect on sustained attention as measured by a CPT in patients with schizophrenia (76). Those homozygous for the high-activity long allele of the 5HTT-LPR displayed impaired attention on the CPT. The molecular outcome of this particular polymorphism is an increased concentration of 5-HTT mRNA and greater 5-HT uptake in long allele homozygotes than in short allele homozygotes (77). Although research examining the effect of serotonin reuptake inhibitors on sustained attention in healthy volunteers does not support their role in improving attention, it is possible that serotonergic drugs may have a specific effect in individuals with genetic variation that produces nonoptimal serotonin reuptake. Other polymorphisms related to serotonergic functioning also appear to be associated with sustained attention, although their functional relevance remains unclear. The T/C polymorphism at codon 102 of the 5-HT2A gene codes for the serotonin 2A receptor, and low expression of the C allele may result in a deficit of 5-HT_{2A} receptor expression (78). Individuals with schizophrenia who were heterozygous for a TC genotype exhibited poor performance on a CPT (79).

Summary

Sustained attention is a critical executive processes that is achieved via the coordinated interaction of top-down frontoparietal areas with brainstem arousal systems. Noradrenaline appears to be a particularly critical neuromodulator of this system, and emerging data suggest that gene variants of this system may explain individual differences in the ability to sustain attention.

Cognitive Neuroscience and Pharmacology of Response Inhibition

Response inhibition is a key executive function central to the ability to modulate and adapt one's behavior in response to changing demands (80,81). Response inhibition is frequently impaired in various conditions, including ADHD, schizophrenia, obsessive-compulsive disorder (OCD), and drug addiction (5,82–84). The stop-signal paradigm measures the cancelation of a response that has already been initiated (80,85). This paradigm involves the establishment of a prepotent response that must be canceled on a minority of trials. For example, in a typical stop-signal task, an individual must respond to the display of the letter X or O by pressing a button corresponding to the letter (the "go" response). For the majority of trials, the go signal is presented alone; however, in a minority of trials (usually 25%), the go signal is followed by a stop-signal (e.g., a red box), indicating that the action should be canceled (Figure 1). Stop-signal inhibition can be viewed as a race between these two competing "go" and "stop" processes. By introducing a delay between the presentation of the go and any subsequent stop signal, one can bias the outcome of the race. When the theoretical assumptions underlying this race model are respected, an index of the "speed of inhibition" can be calculated. This is known as the stop-signal reaction time (SSRT) in which lower values indicate faster inhibition (80,85). Response inhibition can also be assessed with a go/no-go paradigm in which particular stimuli are themselves designated as the stop (or "no-go") event. In the go/no-go task, re-

sponse inhibition can be indexed by the number of incorrect responses made to a no-go event (commission errors) (86).

Functional imaging studies indicate that the right inferior frontal cortex is active during successful response inhibition, with increased activation associated with faster stop-signal reaction times (87). Similarly, human lesion studies report that larger lesions to the right inferior frontal cortex are associated with poorer inhibition (i.e., longer SSRTs) (2). Temporary deactivation of the pars opercularis of the inferior frontal gyrus in humans using transcranial magnetic stimulation also results in longer SSRTs (88).

Although both human lesion and functional MRI studies implicate frontal regions as critical for inhibitory control, research suggests that the basal ganglia may also play an important role. Patients with Parkinson's disease and predominant dopaminergic dysfunction show slower SSRTs not accounted for by generalized motor slowness (89). This deficit can be ameliorated by stimulation of the subthalamic nucleus (STN) of the basal ganglia (90). Further, experimental lesions of the STN in rodents lead to slower SSRTs, indicating impaired inhibitory control (91). Functional MRI data in human subjects also show strong relationships between increased activation in the STN and faster SSRT (92). These lines of evidence suggest that frontostriatal circuits, incorporating the indirect and direct pathways of the basal ganglia may play a specific role in inhibitory control, particularly action cancelation (81,92).

Electrophysiologic studies show that successful response inhibition is characterized by variation of the N2/P3 event-related potential (ERP) waveform, an electrophysiologic response that is seen 200 to 400 msec after stimulus presentation (93,94). Reduced amplitudes of the N2 have been observed in children with ADHD compared with nonclinical children (95), and the N2 and P3 components have also been found to differ significantly from those of healthy individuals in clinical populations with drug addiction (96), depression (97), and obsessive-compulsive disorder (98,99).

Just as our knowledge of the neural circuitry of response inhibition has increased rapidly in recent years, so has our knowledge of its pharmacology. Bari and colleagues (100) examined the effect of modulating noradrenaline, dopamine, and serotonin signaling while rodents performed a stop-signal task. Significant improvements in inhibitory control (shorter SSRT) but not overall speed were seen with the noradrenaline reuptake inhibitor atomoxetine, compared with vehicle. In contrast, a dopamine reuptake inhibitor (GBR-12909) speeded response times but did not alter SSRT. The selective serotonin reuptake inhibitor (SRI) citalopram did not influence speed or SSRT despite other reports in the rodent literature suggesting a relationship between serotonin and motor impulsivity. Nevertheless, some have argued for a role of serotonin in action restraint, as opposed to the action cancelation that is required in the stop-signal task (101). Bari and colleagues argued that because beneficial effects of atomoxetine on SSRT compared with placebo had been reported in human subjects (102,103), noradrenergic mechanisms facilitate response inhibition, whereas dopaminergic mechanisms facilitate faster response speed without enhancing inhibitory control; see also Robinson *et al.* for effect of atomoxetine on SSRT in rodents (104). Furthermore, on the basis of this rodent data, Bari and colleagues asserted that an increase in subcortical extracellular dopamine is neither necessary nor sufficient for ameliorating deficits in stopping performance (100); see also Eagle *et al.* (105).

Human pharmacologic data have yielded a somewhat more contradictory picture. Manipulations of serotonin function in clinical and nonclinical subjects have provided evidence for a role of serotonin in response inhibition. For example, Rubia *et al.* (106) reported that acute tryptophan depletion reduced brain activation in key areas of the response inhibition network, such as the inferior frontal gyrus. A role for serotonin in response inhibition is also implied by work in OCD, a disorder with a putative serotonergic origin and for which response inhibition has been suggested as an endophenotype (83). In line with catecholamine theories of ADHD (107–109), studies have also reported that clinically relevant doses of MPH improve inhibitory control on the stop-signal task in both children (110) and adults with ADHD (111). Nevertheless, inconsistency in the reported effects of stimulants on SSRT have led some to argue that stimulants primarily speed overall go response time and that their effect on SSRT might be baseline-dependent (101,112).

Nandam *et al.* (113) recently conducted the first study in nonclinical human subjects to directly compare clinically relevant doses of MPH, atomoxetine, and citalopram to placebo in a crossover design, while participants undertook the stop-signal task. The results showed that MPH was superior to all other drug conditions and to placebo in improving SSRT, without concomitant changes to response speed. Notably, neither atomoxetine nor citalopram improved SSRT compared with placebo, although there was a trend in that direction for atomoxetine.

Although the dual action of MPH on both dopaminergic and noradrenergic signaling prevents definitive conclusions regarding the pharmacology of inhibition, from the study of Nandam *et al.* (113), comparisons between the pharmacology of MPH and atomoxetine may be instructive. Although MPH and atomoxetine have comparable effects on PFC catecholamine levels, driven largely by reuptake inhibition of the noradrenaline transporter and downstream effects on D1 receptors and $\alpha 2$ receptors (114), their actions dissociate at the level of the striatum where the noradrenaline transporter (NET) is sparse and atomoxetine has limited ability to modulate noradrenaline levels. Nandam *et al.* suggested that the increase in subcortical dopamine occasioned by MPH-induced blockade of DAT may play an important neuromodulatory role. Within the basal ganglia, dopamine might act to transform the top-down catecholamine inputs into a focused, context-dependent signal that is able to suppress or facilitate behavior via the appropriate balance of activity within the indirect or direct pathways, respectively (115). Indeed, there is some evidence that direct infusion of D1- and D2-receptor antagonists into rat striatum has opposing effects on SSRT, with D2 antagonism increasing SSRT (116). Notably, however, no human studies have attempted to modulate SSRT using selective D1/D2 agonists or antagonists, yet such a study is clearly required to confirm a role for dopamine in action inhibition.

Crucially, these pharmacological models of inhibition from both rodent and human work allow important predictions to be made regarding potential molecular targets for genetic association. Thus, allelic variation in prefrontally expressed genes such as those for D1, D4, and $\alpha 2$ receptors as well as NET1, can be tested for association with a response inhibition phenotype in contrast to those predominantly expressed in subcortical regions of the response inhibition network, such as DAT1 and DRD2.

Genetics of Response Inhibition

Evidence from twin studies suggests that measures of response inhibition, such as SSRT derived from the stop-signal task, are highly heritable (6). Indeed, given evidence of impaired response inhibition in nonaffected siblings of probands, it has been argued that inhibition is an endophenotype for both ADHD (82,117) and OCD (83).

Dopamine Gene Polymorphisms and Response Inhibition

A link between dopamine-related gene polymorphisms and response inhibition is not well established, with studies reporting contradictory findings (118). Krämer and colleagues (119) reported that healthy individuals homozygous for the 7-repeat allele of the DRD4 Exon 3 VNTR displayed higher accuracy on a go/no-go task compared with individuals homozygous for the 4-repeat variant. However, studies using clinical samples with ADHD are conflicting, reporting that individuals possessing the 7-repeat allele have either poorer inhibitory control (66) or greater inhibitory control (69) than those without the 7-repeat allele. Congdon *et al.* (120) also reported that nonclinical participants who carried the 7-repeat DRD4 allele had impaired inhibition on the stop-signal task, and this effect interacted with DAT1 genotype such that 7-repeat carriers who were also homozygous for the DAT1 10-repeat allele had elevated SSRTs relative to the other genotype groups.

As discussed earlier, candidate gene studies have repeatedly implicated DAT1 polymorphisms in disorders of executive control such as ADHD (63). As with DRD4, the role of the DAT1 gene in response inhibition is unclear, with little research examining links between polymorphisms of this gene and response inhibition. Cornish and colleagues (121) observed an association between the 10-repeat allele of the DAT1 VNTR and poorer response inhibition in boys aged 6 to 11 who were homozygous for the allele and who scored highly on a teacher-rated report of ADHD symptoms. It has also been suggested that this polymorphism may modulate inhibitory control-related activation as measured with event-related fMRI, although extant findings are inconsistent. In one study, ADHD children and adolescents who were homozygous for the 10-repeat allele showed greater neural activation in the left striatum, right dorsal premotor cortex, and right temporoparietal cortical junction during response inhibition, compared with those who were heterozygous with one 9-repeat allele (122). In contrast, Congdon and colleagues observed greater neural activation associated with carriers of the 9-repeat allele (123). Neither study detected differences in response inhibition performance between homozygotes and heterozygotes.

Congdon and colleagues (123) also examined the Val–Met substitution of the catechol-*O*-methyltransferase (COMT) gene and reported that carriers of the COMT Met allele displayed greater activation during response inhibition than individuals with the Val/Val genotype. The COMT and DAT1 findings here are complementary. For DAT1, the 10-repeat allele is associated with high DAT expression, which may result in an overly efficient uptake of dopamine and decreased dopamine in the synapse. For COMT, the Val allele results in an increased rate of dopamine breakdown by the COMT enzyme and decreased dopamine in the synapse. Both the 10-repeat DAT1 allele and the COMT Val allele were associated with less neural activation during response inhibition, reinforcing the concept that decreased dopaminergic signaling may play a role in impaired response inhibition.

Recently, Cummins *et al.* (in preparation) completed the largest study yet ($n = 412$ nonclinical) to conduct high density SNP mapping across every catecholamine gene and to test association against a response inhibition phenotype. Robust associations that survived corrections for multiple comparisons were seen for markers in the DAT1 gene. Specifically, significant associations were observed for two markers in strong linkage disequilibrium, rs46000 (3.5×10^{-4}) and rs37020 (2×10^{-4}), the former being localized to an intron/exon boundary and the latter to intron six. Interestingly, there was no significant association with the 10-repeat DAT1 allele, and the lack of linkage disequilbrium between either rs46000 or rs37020 and the VNTR suggests a novel and largely independent association. Functional MRI revealed an additive association between allelic variation in DAT1 rs37020 and task-related brain activation during performance of the stop-signal task in both prefrontal and striatal (caudate) regions. These data provide strong evidence for an association with DAT1 variants and are consistent with both the cognitive neuroanatomical and pharmacological models of inhibition reviewed earlier.

Noradrenaline and Serotonin Gene Polymorphisms and Response Inhibition

The limited research into the relationship between gene polymorphisms of the noradrenaline and serotonin systems and response inhibition makes it difficult to draw any conclusions about the potential effect of these polymorphisms on the neurochemical and molecular mechanisms underlying inhibitory control. Candidate gene studies have implicated noradrenergic genes in executive dysfunction disorders such as ADHD (67,124). One study also reported an association between the functional -1021 C/T polymorphism located in the promoter region of the DBH gene and impulsive personality traits in patients with personality disorder (125). However, in contrast with the solid pharmacologic data suggesting a role for noradrenaline in modulating response inhibition, no research has specifically identified associations between noradrenergic gene variants and measures of response inhibition.

As is the case with DAT1, it appears that polymorphisms of the monoamine-oxidase A (MAO-A) gene may influence neural activation during response inhibition, as measured with fMRI, but this does not appear to be recapitulated in a behavioral difference (126). In this case, MAO-A, an enzyme involved in the catabolism of noradrenaline and serotonin, has a VNTR polymorphism in the promoter region that results in high- and low-activity variants. Individuals carrying the high-activity variant showed greater activation during response inhibition in the right ventrolateral prefrontal cortex, whereas individuals carrying the low-activity variant showed greater activation in the right superior parietal cortex and the bilateral extrastriate cortex. However, no behavioral differences were observed between the low-activity and high-activity groups.

In another fMRI study that aimed to elucidate the effects of polymorphisms of the MAO-A and serotonin transporter (5HTT) genes during response inhibition, activation was observed to differ as a function of genotype, whereas behavior did not differ according to genotype (127). When behavioral performance has been directly probed in terms of 5HTT polymorphisms, no association has been found between 5HTT genotype and stop-signal task performance (128).

Tryptophan hydroxylase (TPH) is required for synthesis of serotonin. Variants of the TPH gene have been associated with stop-signal reaction time. An SNP in intron 8 of the TPH2 gene has been shown to be associated with SSRT, with individuals homozygous for the T variant displaying slower SSRT (129). The T allele may be associated with decreased TPH2 functioning and therefore lower levels of serotonin. Baehne and colleagues investigated two SNPs of the gene in relation to the no-go anteriorization of the ERP waveform (130). During response inhibition, the overall spread of the P300 waveform moves in an anterior direction during no-go events when compared with go events. In this study, ADHD and control individuals possessing the T/T genotype of rs11178997 and the G/G genotype of rs4570625 (both SNP genotypes notable as the genotypes preferentially transmitted to ADHD individuals) exhibited reduced no-go anteriorization. Although the effects of these polymorphisms at the level of gene expression have not been shown directly, they appear to be associated with alteration in brain function during response inhibition.

Summary

Response inhibition is instantiated within key nodes of the frontostriatal circuits, with primary neuromodulation achieved by noradrenaline and dopamine. Despite strong evidence for noradrenergic modulation of response inhibition, gene variants of this system have not been heavily implicated. Within the dopamine system, emerging evidence suggests that DNA variation within DAT1, likely acting within subcortical nodes of this network to modulate dopamine availability, predicts individual differences in behavioral and neural measures of response inhibition. DNA variation in the DRD4 gene and response inhibition requires replication but is consistent with a catecholamine modulation of prefrontal circuitry. Although a role for serotonin in stop-signal inhibition is not well indicated by pharmacology, a number of studies have nevertheless reported associations between gene variants such as TPH2 and behavioral and electrophysiologic signatures of response inhibition that now require replication.

Cognitive Neuroscience and Pharmacology of Performance Monitoring and Error Processing

Ongoing task performance is critically dependent on the ability to detect and compensate for errors. This implies the existence of a neural mechanism for monitoring the accuracy of actions and for adjusting behavior accordingly. Rabbitt (131) provided important initial insights into the nature of post-error behavioral adaptation, reporting faster reaction times when subjects committed an error and when an action was executed to correct that error and slower reaction times for responses immediately following the commission of an error. This suggests a compensatory mechanism involving quick error detection and correction, as well as a more careful monitoring of responses to prevent further errors.

The application of electrophysiologic recording to the study of error processing has lead to important insights regarding its neural basis. An ERP known as the error-related negativity (ERN) is observed to peak 0 to 100 msec after an erroneous response (132). An extensive literature now indicates that the ERN does not directly reflect error detection but rather performance monitoring processes that are sensitive to response conflict (133) and changes in reward probability (134). Another ERP relevant to error processing is the error positivity, a positive-going potential following the ERN that is only present on error trials during which the person is consciously aware of having made an error (135). The ERN and error positivity therefore provide useful electrophysiologic signatures for probing the various components of error processing.

Holroyd and Coles (134) interpreted the performance monitoring system in terms of reinforcement learning, thereby implicating the mesencephalic dopamine system. This system is involved in assigning a valence to a behavior so that incorrect behavior (such as committing an error) is associated with a negative outcome, and is therefore less likely to be performed again in the future. According to this model, the anterior cingulate cortex (ACC) acts as a control filter for incoming information about potential motor responses originating from various controllers that attempt to exert an influence over the motor system. The ACC receives reinforcement learning signals from the basal ganglia for it to prioritize a particular motor controller. The role of the basal ganglia in this system is to associate a value to ongoing events, such as stimuli and responses during a task, and to indicate whether the outcome of a response is better or worse than expected. In this context, an error would be interpreted as an outcome that is worse than expected. Holroyd and Coles postulated that errors result in a phasic decrease in mesencephalic dopaminergic activity, which in turn disinhibits the neurons of the ACC, thereby generating the ERN. Indeed, functional MRI studies have consistently identified the ACC as having role in error processing, with increased ACC activation observed following incorrect responses (136,137), and EEG source analysis has supported the ACC as the generator of the ERN (138,139). Much research assessing the influence of midbrain dopaminergic function on performance monitoring has been conducted in patients with Parkinson's disease (PD). PD is associated with predominant loss of nigrostriatal dopamine neurons and depletion in dopamine activity. PD patients display impaired performance on tasks involving reward-based learning (140), suggesting that if error processing is dependent on reinforcement learning, dopamine may play an integral role. Three studies have reported that PD patients exhibit a smaller ERN compared with matched control subjects across various tasks (141–143), suggesting an impairment of performance monitoring. This finding has been observed in patients on and off medication (142,143). One study also reported that error correction was also lower in the PD group (141). Differences in the ERN between PD and control subjects have not, however, been detected in all studies (144). One of the challenges in this area is the potential for other factors such as disease severity or other cognitive or motoric deficits to influence error processing in PD patients (144). It should also be noted that because patients with PD also experience cell loss in the locus coeruleus/noradrenergic system, and this system is responsive to errors (145), caution must be exercised in using PD as an exclusively dopaminergic model.

Error processing has also been investigated in ADHD; see Shiels and Hawk for review (146). In an ERP study of ADHD and healthy control children performing a flanker task, ADHD children made more errors than control subjects; MPH normalized the error rate and error positivity but did not alter ERN amplitudes compared with placebo (147). It is unclear why MPH had no detectable effect on the ERN. Neural circuitry underpinning performance monitoring may depend on developmental stage (148,149). As mentioned previously, the error positivity is thought partly to reflect error consciousness (135,150). An increased awareness of errors may account for the reductions in error rate observed in ADHD children who were treated with MPH. D-amphetamine, also used to treat ADHD, increases ACC activity in healthy individuals (151). Compared with placebo, administration of D-amphetamine to healthy individuals resulted in a selective enlargement of the ERN amplitude on the flanker task, suggesting an effect of D-amphetamine on performance monitoring (152). Although MPH and D-amphetamine are widely used in clinical practice, they are not selective drugs, enhancing both dopaminergic and noradrenergic signaling (153). Thus, these findings do not permit identification of specific neurotransmitters involved in error processing.

Other studies suggest a potential role for dopamine in modulating error processing. Cocaine abuse is associated with decreased D2 receptor availability (154,155) and decreased sensitivity to adverse consequences (156). During the flanker task, cocaine-dependent individuals displayed reduced ERN and error positivity compared with control subjects, as well as less improvement in accuracy post errors (157). Two studies have investigated the impact of the D2 antagonist haloperidol on indexes of performance monitoring in healthy volunteers. Compared with placebo, participants receiving haloperidol committed more errors, displayed attenuated ERNs, and had impaired learning on a time-estimation task (152,158).

Little research has investigated the explicit role of noradrenaline in performance monitoring and error processing. Despite the established role of noradrenaline in a range of executive processes, as reviewed earlier (159), few studies have investigated the impact of manipulating noradrenergic signaling on performance monitoring.

The ACC is innervated by noradrenergic fibers projecting from the locus coeruleus (145), providing a possible neuroanatomic basis for a noradrenergic effect. On a behavioral level, the α2A adrenoreceptor antagonist guanfacine has been shown to improve error rates in ADHD children performing a continuous performance task (160). Administration of the α2 antagonist yohimbine to healthy volunteers resulted in an increase in the amplitude of the ERN and a significant decrease in the number of errors committed during a flanker task (161). Although yohimbine can act on serotonin and dopamine receptors in addition to α2 receptors (162), research indicates that yohimbine increases firing in the locus coeruleus (163) and leads to noradrenaline release at the synapse (164).

Individuals with depression are sensitive to negative environmental cues such as errors and may magnify the significance of errors (165). Patients with major depressive disorder (MDD) display a larger ERN compared with healthy control subjects (166). Functional connectivity analyses demonstrate that in healthy individuals, commission errors lead to specific activation of frontal regions (rostral ACC and medial PFC at 80 msec, dorsolateral PFC at 472 msec). Individuals with MDD do not exhibit this post-error recruitment of PFC-based cognitive control (166). This suggests that MDD is associated with altered error processing. Despite these findings in depression, pharmacologic investigations of error processing and performance monitoring have largely discounted a role for serotonin. Mirtazapine, an antidepressant that enhances activity of both noradrenaline and serotonin, had no effect on ERN amplitude (152). The SRI paroxetine also had no effect on ERN compared with placebo in healthy volunteers (167).

Investigating the association between serotonergic activity and performance monitoring using acute tryptophan depletion (ATD) has revealed that ATD modulated the blood oxygen level–dependent response in the dorsomedial PFC (dmPFC) during performance monitoring in a go/no-go task, although no behavioral change was detected (168). The dmPFC, located close to the ACC, has not been associated with error detection but is believed to be involved in improving task performance following errors. Inactivation of the dmPFC results in the attenuation of the post-error slowing in rats (169), potentially implicating it in performance monitoring. This is in line with the evidence from another study employing ATD in conjunction with EEG and a time-estimation task, which found no effect of ATD on feedback-related negativity, which is elicited by feedback regarding accuracy (170). For the most part, ATD appears to exert its influence through an effect on negative feedback processing (171).

Genetics of Performance Monitoring and Error Processing

A genetic component to performance monitoring and error processing has been suggested through studies of ADHD individuals, their biological relatives, and control subjects. Albrecht and colleagues (172) tested boys with ADHD, their nonaffected siblings, and control subjects using a flanker task. A decreased ERN in the ADHD children compared with healthy control subjects was revealed on EEG, and the nonaffected siblings of the ADHD children displayed ERN amplitudes in the intermediate range between those of the ADHD and control groups. This suggests an ADHD familial risk profile for performance monitoring and error processing that warrants further investigation. Although research into the possible effect of genetic polymorphisms on error processing is limited, several studies are noteworthy.

Krämer and colleagues (173) investigated the impact of polymorphisms of COMT and DRD4 on performance monitoring and error processing using ERP and the flanker task with an embedded stop-signal component, allowing for both choice errors and stop errors. A larger ERN was observed after stop errors for participants with the Val/Val COMT genotype (i.e., those with lesser prefrontal dopamine levels) compared with those with the Met/Met genotype. For the -521 promoter SNP of DRD4, T-allele homozygotes displayed an increased ERN after choice and stop errors when compared with C-allele carriers. These participants also displayed higher post-error slowing as a compensatory mechanism for the error of commission. The T allele has also been associated with a decrease in transcriptional efficiency of 40% compared with the C allele (174). However, the functional outcome of the -521 SNP is far from clear, with other studies reporting a lack of association between this SNP and mRNA expression in postmortem tissue (175) or between the SNP and transcriptional activity in vitro (176).

The effect of gene polymorphisms on performance monitoring can also be investigated using probabilistic learning tasks. These tasks are based on the reinforcement model of learning in which responses are monitored in an ongoing way to assess whether the outcomes are better or worse than expected. A probabilistic learning task has been used to investigate the involvement of the DRD2 TaqIA polymorphism of the dopamine D2 receptor gene in performance monitoring. The A1 allele of the TaqIA polymorphism is associated with a reduction in D2 receptor density in the striatum and caudate (177–179). Klein and colleagues (180) demonstrated that A1 allele carriers were less efficient at learning to avoid actions that had negative consequences. These individuals also had diminished functional activation after receiving feedback about an incorrect action in the posterior medial frontal cortex, the region involved in feedback monitoring. An ERP study by Althaus and colleagues (181) did not find an association between the ERN and DRD2 TaqI genotype in children, although an interaction was detected between the TaqIA polymorphism and the VNTR of the serotonin transporter gene (5-HTTLPR). The short variant of the 5-HTTLPR is associated with low serotonin activity. Children carrying both the DRD2 TaqIA variant and the short 5-HTTLPR variant exhibited a greater ERN than children of other genotypes. This larger ERN was also associated with the short 5-HTTLPR variant, independent of DRD2 TaqI genotype.

The influence of the short 5-HTTLPR variant on the ERN has been observed in other studies independent of DRD2 genotypes. ERP research revealed that healthy individuals with at least one copy of the short variant showed significantly higher ERN amplitudes and a trend toward higher error positivity amplitudes compared with long-allele homozygotes, despite no measured behavioral differences (182). Holmes, Bogdan, and Pizzagalli (183) investigated the impact of allelic variation in the VNTR of 5-HTTLPR on error processing. Using a modified flanker task known to induce errors, it was found that individuals with the short variant of the VNTR displayed impaired post-error behavioral adjustments, as well as a larger error-related ACC activation, compared with individuals with the long variant, consistent with previous EEG results (182).

Another study further implicated serotonergic transmission in performance monitoring, with variants of the functional serotonin 1A receptor polymorphism modulating performance on the flanker task (184). This polymorphism affects serotonergic function, with the -1019 G allele disinhibiting the autoreceptor expression and reducing serotonergic neurotransmission (185). Carriers of at least one G allele displayed smaller ERNs and decreased post-error slowing relative to C homozygotes. These findings were specific to the commission of errors, because there was no effect of genotype on other measures of performance monitoring, such as the correct response negativity, a negative potential that follows the execution

of a correct response on a task. The G allele has been associated with higher 5-HT 1A receptor binding potential in the raphe nuclei, amygdala and hippocampus of patients with bipolar disorder (186), suggesting a negative effect of this altered 5-HT 1A binding on error processing that could potentially be improved pharmacologically.

Summary

The study of performance and error monitoring is a burgeoning area of interest within cognitive neuroscience and psychiatry. Evidence from functional neuroimaging shows that errors reliably elicit activity in the dorsal ACC, whereas EEG studies have identified stereotypical waveforms associated with errors including the ERN and error positivity (Pe). The ERN, which has been sourced to the dorsal ACC, likely reflects performance monitoring processes that are sensitive to response conflict and reward probability, with evidence suggesting that this component is modulated by both dopamine and serotonin in paradigms requiring reinforcement learning and/or probabilistic learning (104). In line with these expectations polymorphisms of both the dopamine (TaqIA of DRD2) and serotonin systems (5-HTTLPR) and their interaction have been associated with ERN amplitudes during probabilistic learning tasks. The Pe is thought to represent a response-locked equivalent of the P3 for which strong links to catecholamines have been established. Associations between noradrenergic system genes and the amplitude of the Pe are predicted by cognitive neuroscience models, but not yet documented.

Conclusions

It should be apparent from this review that cognitive neuroscience is interfacing with molecular genetics as never before. Cognitive neuroscientists have seized on the opportunities provided by the sequencing of the human genome to interrogate the molecular genetic substrates of cognitive processes such as sustained attention, response inhibition, and error processing. To date most studies have employed hypothesis-driven candidate gene approaches in which the choice of gene is predicated on known brain-behavior and neurochemical substrates for the cognitive process. With respect to executive functions, this relatively new field has focused heavily on monoamine gene variants given the well-established neuromodulatory influence of the monoamines over executive function.

Within this literature, associations between DNA variants of the DBH gene and measures of sustained attention accord well with cognitive-neuroanatomic models of sustained attention and the known noradrenergic modulation of sustained attention. The observation that DBH is a risk gene for ADHD and that sustained attention deficits are familial in ADHD, raises the possibility that the DBH–ADHD relationship may be mediated or moderated via the effects of the gene on sustained attention and its neural networks.

With respect to response inhibition, there is intense international interest in identifying genetic predictors of individual differences in response inhibition, itself a potential endophenotype for ADHD, OCD, and addiction. Although we are aware of several large-scale, multisite studies employing both behavioral and neural indexes of response inhibition with a view to performing GWAS, no such published studies currently exist. As highlighted in this review, abundant evidence suggests that catecholamine function and frontostriatal circuitry is critically important to our ability to brake and inhibit behavior. Emerging findings from candidate gene studies of response inhibition highlight novel associations with allelic variants of the DAT1 gene that show promise of reliably predicting individual differences in inhibitory ability. Evidence also suggests that variants of the DRD4 gene, including the much studied Exon 3 VNTR, may be associated with this phenotype, although the results are less consistent across studies.

Performance monitoring is a burgeoning area of study within cognitive neuroscience, but there is a dearth of either behavioral or molecular genetic studies addressing this phenotype. As discussed, there is robust evidence that error and/or reinforcement learning signals are encoded by midbrain dopaminergic inputs to areas such as the anterior cingulate. Strong evidence also suggests that serotonin may modulate related processes such as probabilistic learning. Preliminary molecular genetic work suggests that variants of both the dopamine (TaqIA of DRD2) and serotonin systems (5-HTTLPR) and their interaction might associate with amplitudes of the ERN during probabilistic learning tasks, for example. No studies have systematically tested for association with performance monitoring phenotypes (behavioral or physiological) across the full range of monoamine genes, yet clearly this would be instructive.

Taken together, the molecular genetic associations between monoamine gene variants and either sustained attention, response inhibition, and error processing phenotypes, largely recapitulate the underlying biology of these processes. Thus, associations between gene variants of DBH and sustained attention, between DAT1 and response inhibition, and between DRD2 and 5-HTT, are predicted by current models from cognitive neuroscience.

The literature reviewed here offers tantalizing insights into the molecular genetics of executive control, built strongly on advances in our knowledge of the neuroscience of executive control. However, cognitive neuroscientists have not typically sought the degree of replication that has now become standard in other fields such as psychiatric genetics. Legitimate concerns regarding Type 1 error need to be allayed by seeking replication from independent laboratories and statistically controlling for multiple comparisons. As should be apparent from this review, multiple neurotransmitter systems are implicated in each of the executive phenotypes discussed. Despite this, few studies have attempted systematic screens of entire gene systems, yet clearly this would be beneficial to provide a context for any reported associations. If cognitive neuroscientists are to advance this field and avoid a body of work that generates more heat than light, we will need to apply the same scientific rigor that is being demonstrated in the field of psychiatric genetics. Greater rigor and certainty will enable the field to embrace important questions such as how genetic variants might have prognostic value for predicting outcome in disorders of executive function or how cognitive rehabilitative strategies could perhaps be targeted to individuals with known risk genotypes.

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