Published in final edited form as:
Pharmacol Biochem Behav. 2014 August ; 0: 45–54. doi:10.1016/j.pbb.2013.08.007.

The Neural and Genetic Basis of Executive Function: Attention, Cognitive Flexibility, and Response Inhibition

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Abstract

Executive function is a collection of cognitive processes essential for higher order mental function. Processes involved in executive function include, but are not limited to, working memory, attention, cognitive flexibility, and impulse control. These complex behaviors are largely mediated by prefrontal cortical function but are modulated by dopaminergic, noradrenergic, serotonergic, and cholinergic input. The ability of these neurotransmitter systems to modulate executive function allows for adaption in cognitive behavior in response to changes in the environment. Because of the important role these neurotransmitter systems play in regulating executive function, changes in these systems can also have a grave impact on executive function. In addition, polymorphisms in genes associated with these neurotransmitters are associated with phenotypic differences in executive function. Understanding how these naturally occurring polymorphisms contribute to different executive function phenotypes will advance basic knowledge of cognition and potentially further understanding and treatment of mental illness that involve changes in executive function. In this review, we will examine the influence of dopamine, norepinephrine, serotonin, and acetylcholine on the following measures of executive function: attention, cognitive flexibility, and impulse control. We will also review the effects of polymorphisms in genes associated with these neurotransmitter systems on these measures of executive function.

Keywords

cognition; attention; impulsivity; dopamine; acetylcholine; prefrontal cortex; norepinephrine; serotonin

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Introduction

All individuals must be able to adapt to ever-changing environments in order to survive. The ability to adapt by regulating reflexive reactions to current salient stimuli so that goals requiring complex behaviors can be attained has been labeled executive function. Executive function is theorized to be a group of higher order cognitive abilities that enable individuals to orient towards the future, demonstrate self-control, and successfully complete goal directed behavior (Baddeley 1998; Robbins 1996; Stuss and Alexander 2000). The higher order cognitive processes thought to comprise executive function include impulse control, response inhibition, attention, working memory, cognitive flexibility, planning, judgment, and decision-making (Baddeley 1998; Robbins 1996; Stuss and Alexander 2000). In humans and other animals executive function is disrupted following brain injury involving the frontal cortical regions (Bechara and Van Der Linden 2005; Schoenbaum et al. 2006). Furthermore, there are numerous psychiatric disorders that are characterized by disruptions in executive function; schizophrenia, attention deficit hyperactivity disorder, bipolar disorder, substance abuse, antisocial behavior and obsessive-compulsive disorder (Brower and Price 2001; Cavedini et al. 2006; Daban et al. 2006; Schoenbaum et al. 2006; Willcutt et al. 2005). Effective demonstration of executive function can be identified as intelligent behavior (Duncan et al. 2000) and is required for normal functioning in everyday life; thus it is clear why altered executive function would have a grave impact on mental health.

The importance of executive function in everyday life is highlighted by the well-known case of Phineas Gage, the railroad foreman who survived an accident in which a tamping iron passed through his skull and frontal lobe but underwent a transformation from a responsible, socially adjusted individual to a derisive and unpredictable individual (Damasio 1994). In general, people with damage to the frontal lobes demonstrate poor control and regulation over their behavior and usually do not function well in their everyday lives. Frontal lobe patients have consistently demonstrated impairment on complex tasks, such as the Wisconsin Card Sorting Test and the Tower of Hanoi task, which require intact executive function, even though the patients may demonstrate intact performance on other cognitive tasks such as IQ tests (Damasio 1994). Poor performance on complex executive tasks can be due to deficits in one or more of the higher order cognitive processes that may be involved in complex executive function. As research on the role of the frontal lobe in executive function progressed, a clear association emerged between specific areas of the frontal lobe and the individual cognitive processes that sub-serve executive function. This review will focus on four cognitive processes that participate in executive function: response inhibition, attention and two types of cognitive flexibility, set-shifting, and reversal learning; and the neurochemical circuitry in the prefrontal cortex (PFC) associated with these processes. Numerous reviews of working memory and PFC circuitry have recently been published (Arnsten et al. 2012; Cools and D'Esposito 2011; Gamo and Arnsten 2011; Scheggia et al. 2012; Stormer et al. 2012); thus this cognitive process will not be included in the current review. We will provide an overview of the neurochemical circuits in the PFC, focusing specifically on the dopamine, serotonin, norepinephrine, and acetylcholine transmitter systems and review recent research establishing pharmacogenetic associations between function of the PFC and set-shifting, attention, response inhibition and reversal learning.

Prefrontal cortex: Neurochemical Circuitry and Role in Executive Function

Although the degree of complexity in the prefrontal cortex is significantly different between humans, non-human primates and rodents, there is sufficient homology in the neuroanatomical and neurochemical circuitry between the species to allow for a general description of the circuitry of the PFC. The PFC includes several distinct areas of the frontal cortex including the anterior cingulate cortex, prelimbic cortex, infralimbic cortex, dorsal peduncular cortex, dorsolateral orbital cortex, lateral orbital cortex, and ventral orbital cortex. Based on structural and function data these areas within PFC can be grouped to form subregions of PFC; specifically medial prefrontal cortex (mPFC) and orbital frontal cortex (OFC). The mPFC includes anterior cingulate cortex, prelimbic cortex, infralimbic cortex, and dorsal peduncular cortex while the OFC consists of the dorsolateral, lateral, medial, and ventral orbital cortices (Groenewegen and Uylings 2000; Robbins 2000; Teffer and Semendeferi 2012). The mPFC and OFC receive input from the dopamine (DA), norepinephrine (NE), serotonin (5-HT), and acetylcholine (ACh) neurotransmitter systems and differ slightly in the origin of afferent projections and destination of efferent communication.

The homology in the anatomy of the PFC is paralleled by homology in the specific cognitive processes attributed to these cortical areas (non-human primates - (Robbins 1996); rodents - (Dalley et al. 2004; Kesner and Churchwell 2011)). The executive function processes of response inhibition, attention, set-shifting and reversal learning can themselves be differentiated into more specific processes or functional attributes such as sustained versus selective attention, rule selection and strategy switching for set-shifting and perseveration and strategy switching for reversal learning. These very specific functional attributes can be task dependent. Thus the functional attributes associated with specific prefrontal cortical areas may seem to vary between humans, non-human primates and rodents because the types of tasks used to test the specific cognitive processes that comprise executive function are different between the species. However, some tasks have been designed to be translational across species, for example the continuous performance test used in humans to assess attention has been adapted to non-human primates (Weed et al. 1999) and to rodents (Robbins 2002) as the 5-choice serial reaction time test (5CSRT). Based on data from these translational tasks, the essential assessment of attention is consistent across species even though the direct behavioral measures are different.

As damage to Phineas Gage's frontal lobe was associated with specific deficits in executive function, lesion studies in rodents have delineated which areas of PFC are required for performance of specific cognitive abilities. Response inhibition is disrupted with lesions of OFC while removal of mPFC had no effect (Eagle et al. 2008). Disruption of attention is evident with lesions of mPFC (Maddux and Holland 2011) while OFC lesions had no effect on attention but did disrupt response inhibition measured in the same task (Chudasama et al. 2003). Reversal learning was normal while set-shifting was disrupted after removal of mPFC (Birrell and Brown 2000; Bissonette et al. 2008; Floresco et al. 2008; McAlonan and Brown 2003). Removal of OFC caused deficits in reversal learning while having no effect on set-shifting (McAlonan and Brown 2003). Based on the research just reviewed, the mPFC is responsible for attentional processing and for cognitive flexibility requiring set-

shifting whereas the OFC regulates the cognitive flexibility required for reversal learning and response inhibition. The subsequent sections will describe the role of the DA, NE, 5-HT and ACh systems in the mPFC mediation of attention and set-shifting and the OFC regulation of response inhibition and reversal learning.

The Dopamine System: Circuitry and role in Executive Function

Dopamine is involved in many processes in addition to executive function such as encoding rewards and drug addiction (Everitt et al. 1999; Grace 1995; Koob 1992). The mPFC and OFC receive dopamine input from the ventral tegmental area (VTA) and express multiple dopamine receptor subtypes, D1, D2, D3, and D4 (Gaspar et al. 1995; Wedzony et al. 2000) although expression of D3 receptors is very low (Levesque et al. 1992). Pyramidal neurons in the mPFC primarily express D1 receptors but some D2 and D4 receptors are also expressed (Gaspar et al. 1995). In contrast, GABAergic interneurons in non-human primates express equivalent levels of D1, D2 and D4 receptors (Mrzljak et al. 1996). Some D1, D2 and D4 receptors may also be expressed on presynaptic excitatory glutamate terminals (Mrzljak et al. 1996; Wedzony et al. 2000).

While mPFC and OFC have the same dopaminergic afferents, their efferents to the midbrain differ somewhat in rats. Although, mPFC and OFC project directly to the VTA and the periaquaductal grey (PAG) (Geisler et al. 2007; Hoover and Vertes 2011) their functional regulation of the VTA differs. Projections from mPFC can either excite or inhibit activity in the VTA while the OFC only has an inhibitory effect in the VTA in rats (Lodge 2011). Thus, the mPFC can differentially regulate its own dopaminergic activity while the OFC can only inhibit the activity of the neurons providing DA input. Excitatory regulation of VTA dopaminergic activity by projections from the mPFC may explain why set-shifting and attention are associated with DA activity in the mPFC while response inhibition and reversal learning are not dependent on DA activity in the OFC.

Poor performance in set-shifting and attention tasks is seen when mPFC DA activity levels are low while increases in DA activity improves set-shifting and attention. Pharmacological depletion of DA disrupted set-shifting and attention measured simultaneously in a set-shift task in non-human primates and rodents (Crofts et al. 2001; Robbins and Roberts 2007). Dopamine D1 and D2 receptors both play a role in set-shifting in rats as evidenced by the disruption of set-shifting following infusion of selective antagonists into mPFC (Floresco et al. 2006; Ragozzino 2007). In contrast to disruptive effects of D1 and D2 receptor antagonism, a selective antagonist of D4 receptors in mPFC improved set-shifting while a selective D4 agonist disrupted set-shifting (Floresco et al. 2006). The ability of an increase in DA activity at the D4 receptor to disrupt set-shifting could be due to the differential expression levels of D1 and D4 receptors on pyramidal neurons relative to GABAergic interneurons.

Under normal levels of DA transmission, the activity of pyramidal cells is driven primarily by excitatory D1 receptor-mediated processes with the inhibitory D4 receptors providing a slight down regulation of pyramidal cell activity. The activity of GABAergic interneurons is balanced by excitatory influence via D1 receptors and inhibitory influence of D4 receptors. When D1 and D4 receptors are functioning properly on GABAergic interneurons, a

balanced GABAergic regulation of pyramidal cell output occurs. This regulation of PFC pyramidal neuron output by GABAergic interneurons is required for optimal functioning (Lewis and Moghaddam 2006). Agonism of D4 receptors could disrupt set-shifting through increased inhibition of pyramidal cells that would decrease their firing rate and/or increased inhibition of GABAergic interneurons, which could dysregulate the pyramidal neuron firing.

Pharmacological manipulations that increase mPFC DA activity are associated with improvement in set-shifting and attention. Increasing synaptic DA by inhibiting catecholamine-omethyl-transferase (COMT), the enzyme responsible for degradation of DA, improved set-shifting in humans (Apud et al. 2007) but failed to improve set-shifting in rats (Tunbridge et al. 2004). Direct activation of mPFC D1 receptors improved the attentional component of a combined attention and memory task as measured in rats (Chudasama et al. 2004) and modulation of D4 receptors affected cognitive flexibility. In marmosets and rats, antagonism of the mPFC D4 receptors improved cognitive flexibility (Clarke et al. 2005; Floresco et al. 2006).

Dopamine transmission in the OFC does not play a role in reversal learning in non-human primates (Roberts et al. 1994), although it is involved in other processes such as decision-making in tasks concerned with reward in rats (Floresco and Magyar 2006; Kheramin et al. 2004; Winstanley et al. 2006). While there are no published reports of DA in OFC affecting response inhibition as measured with go/no-go or stop signal tasks, DA activity in areas such as parietal cortex, measured with fMRI, is associated with performance on these tasks (Hershey et al. 2004). Dopamine activity in rodent OFC is involved in involuntary response inhibition of the type assessed in pre-pulse inhibition of the acoustic startle reflex (Zavitsanou et al. 1999).

In summary, the importance of DA neurotransmission to the cognitive processes sub-serving executive function differs across areas of PFC and the neurocircuitry of the mPFC and OFC also exhibit differences which can explain the different contributions to cognitive processes. In mPFC, DA activity plays a major role in mediating set-shifting and attention with higher levels of DA associated with optimal performance of these cognitive processes. In contrast, DA activity in the OFC is not required for the demonstration of response inhibition or reversal learning.

The Norepinepherine System: Circuitry and role in Executive Function

The locus coeruleus (LC) is the primary source of NE projections to the mPFC and OFC. Norepinepherine receptors, α1-, α2-, and β-receptors, are localized presynaptically on noradrenergic axons in the mPFC and OFC and α2-receptors are also found on postsynaptic neurons (U'Prichard et al. 1979). Of the three subtypes of α2-receptors, α2A, α2B and α2C, the α2A subtype is most prevalent in PFC. The α2A receptor is expressed presynaptically on noradrenergic terminals and postsynaptically on pyramidal cells (Aoki et al. 1998). Activation of the different NE receptor types is dependent on the arousal level of the individual monkey, with α2-receptors engaged at normal arousal levels (Li and Mei 1994) and α1-receptors engaged at stressful levels of arousal in monkeys and rats (Ramos et al. 2005). The efferent projections from the mPFC and OFC differ. In rats, the mPFC projects

to the LC while the OFC does not (Hoover and Vertes 2011). Thus only the mPFC can directly regulate LC activity.

While DA activity was associated with set-shifting and attention but not response inhibition or reversal learning, NE activity impacts all four of the cognitive process that sub-serve executive function. Set-shifting and attention are impaired when mPFC NE activity levels are low. In rats, lesions producing substantial decreases in mPFC NE impaired attention (Milstein et al. 2007) and set-shifting (McGaughy et al. 2008; Tait et al. 2007) and this deficit was reversed by the selective NE reuptake inhibitor, atomoxetine (Newman et al. 2008). In normal monkeys and rats, improvements in set-shifting were produced with systemic administration of drugs that increase synaptic levels of NE, methylphenidate, desipramine, and atomoxetine (Lapiz et al. 2007; Seu and Jentsch 2009; Verrico et al. 2008). The fact that the NE selective reuptake inhibitor atomoxetine was as effective as the non-selective reuptake inhibitors, methylphenidate and desipramine, suggests that the increased levels of DA and 5-HT seen with non-selective reuptake inhibitors were not responsible for the improvement in set-shifting. Additional support for the specific role of NE activity in set-shifting comes from the finding that administration of a selective α-2-adrenergic autoreceptor antagonist improves set-shifting (Lapiz and Morilak 2006). Lapiz and Morilak (2006) also demonstrated that the improvement in set-shifting was reversed by mPFC infusion of a postsynaptic α-1 receptor antagonist.

There is also evidence for the efficacy of NE reuptake inhibitors and selective adrenergic agonists in improving attention in the 5CSRT in rats. Selective NE reuptake inhibitors, atomoxetine and reboxetine, consistently improved measures of attention in the 5CSRT as well as improving response inhibition (Navarra et al. 2008; Paterson et al. 2011; Robinson 2012) while non-selective reuptake inhibitors, methylphenidate and desipramine, improved attention in poor performing animals and under attention loading task parameters but had inconsistent effects on response inhibition (Navarra et al. 2008; Paterson et al. 2011; Robinson 2012). Selective β1- and β2- adrenergic agonists, dobutamine and clebuterol, also improved attention with the β2 adrenergic agonist also improving response inhibition (Pattij et al. 2012).

Increased OFC NE activity has been associated with improved response inhibition and reversal learning. A large number of studies have evaluated the impact of NE activity in OFC on response inhibition (for review see (Eagle et al. 2008)). In rats, increasing synaptic levels of NE with atomoxetine improved inhibitory response control (Bari et al. 2009; Robinson et al. 2008) without altering reaction time on correctly initiated responses (Robinson et al. 2008). The role of OFC NE activity on reversal learning has also been evaluated. Drugs that inhibit the NE transporter, methylphenidate, desipramine, and atomoxetine, improved reversal learning (Seu and Jentsch 2009). The selective α2-adrenergic agonists' guanfacine and medetomidine also improved reversal learning in a dose dependent manner in monkeys and rats (Steere and Arnsten 1997; Tanila 1993).

Unlike the specific role mPFC DA activity plays in set-shifting, NE activity has an impact on all four of the cognitive processes that sub-serve executive function. The importance of NE activity in both mPFC and OFC in modulating executive function could be due to the

general role of NE in regulating overall arousal level and setting basal levels of cortical activity when an individual is performing all four of the cognitive processes. The fact that the activation of different NE receptor types is dependent on the arousal level of the individual provides the mechanism for the ability of the NE system to play a role in modulating cognitive processes. Specifically, the NE system would be able to optimize function relative to the state of the environment and the individual at the time of testing.

The Serotonin System: Circuitry and role in Executive Function

The dorsal raphe (DR) is the primary source of 5-HT projections to the mPFC and OFC. Of the seven subfamilies of 5-HT receptors, the PFC expresses only the 5–HT1, 5-HT2 and 5-HT3 receptor subfamilies and their expression level varies across cortical layers and neuronal cell type. PFC pyramidal neurons in rats express the inhibitory 5-HT1A receptor and the excitatory 5-HT2A and 5-HT2C receptors (Pompeiano et al. 1992; Pompeiano et al. 1994; Puig et al. 2010) and a majority of these neurons co-express 5-HT1A and 5-HT2A receptor subtypes (Puig et al. 2010; Santana et al. 2004). In primates and rodents, GABAergic interneurons in the PFC express 5-HT1A, 5-HT2A, or 5-HT3A receptors (de and Mengod 2007; Vucurovic et al. 2010; Weber and Andrade 2010; Willins et al. 1997; Zhou and Hablitz 1999). The axon terminals of glutamate and GABA neurons also express 5-HT receptors whose function it is to regulate impulse-dependent release of glutamate and GABA in rodents (Mathur et al. 2011; Torres-Escalante et al. 2004; Zhou and Hablitz 1999). In rodents, 5-HT1B receptors are typically expressed on presynaptic terminals in the brain (Boschert et al. 1994; Sari et al. 1999), but in the PFC it is not clear what receptor subtype is responsible for presynaptic serotonergic regulation of transmitter release.

Both the mPFC and OFC have efferent projections to the dorsal raphe thereby allowing both mPFC and OFC to regulate 5-HT activity (Enge et al. 2011). In rats, indirect regulation of activity in the DR occurs via the 5-HT2A receptors expressed on the pyramidal neurons projecting to the DR (Vazquez-Borsetti et al. 2009). Although GABAergic interneurons in the PFC also express 5-HT2A receptors and play a role in regulating pyramidal cell activity, the activation of cortical 5-HT2A receptors can increase cortical excitatory input in the DR (Vazquez-Borsetti et al. 2009). In addition, there is a 5-HT1A feedback mechanism in which 5-HT may inhibit cortical GABAergic interneurons via activation of 5-HT1A receptors. This would release cortical glutamatergic neurons that synapse on GABAergic neurons in DR and thus decrease DR output (Sharp et al. 2007). The 5-HT modulated projection neurons from the mPFC innervate the VTA as well as well as the DR in rats (Vazquez-Borsetti et al. 2011) thereby allowing for coordination of the activity of the dopaminergic and serotoninergic systems by the mPFC.

As reviewed by Cools et al. (2008), serotonergic activity in the OFC is associated with degree of response inhibition and performance on reversal learning tasks. In the OFC, 5-HT activity is strongly associated with response inhibition as seen in rats lacking the 5-HT transporter who have high levels of 5-HTand increased response inhibition (Homberg et al. 2007). In addition, low levels of 5-HT resulted in an inability to inhibit prepotent responses in marmosets (Walker et al. 2006). Another example of the impact of low levels of 5-HT in the OFC is a study in which humans with dietary-induced tryptophan-depletion performed a

go/no-go response task (Crockett et al. 2009). No slowing of responses on no-go trials was seen in tryptophan-depleted individuals indicating a deficit in inhibitory control.

In addition to disrupting inhibitory control, 5-HT depletion in the OFC produces substantial deficits in reversal learning in monkeys and rats (Clarke et al. 2004; Clarke et al. 2005; Clarke et al. 2007; Lapiz-Bluhm et al. 2009). Similar effects of 5-HT depletion are seen in humans, with acute tryptophan depletion in healthy volunteers slowing responding in a reversal learning task (Murphy et al. 2002). However, one rat study failed to find an effect of acute tryptophan depletion on spatial reversal learning (van der Plasse and Feenstra 2008). This lone result suggests that the role 5-HT activity has in reversal learning may be dependent on the type of stimuli involved in the task, with visual but not spatial reversal learning requiring 5-HT activity. The issue of whether spatial versus visual reversal learning are different and involve different neurotransmitter systems requires further examination. In the PFC, 5-HT depletion did not impact performance on a set-shifting task although the depletion caused a deficit in reversal learning (Clarke et al. 2005; Lapiz-Bluhm et al. 2009) nor did it have a detrimental effect on attention in mice (Alkam et al. 2011).

In summary, the 5-HT system plays a crucial role in the OFC in mediating response inhibition and reversal learning with low levels of serotonin associated with poor response inhibition and deficits in reversal learning. In contrast, serotonin in the mPFC is not integral performance of set-shifting or attention. Whereas DA activity in the mPFC is crucial to set-shifting and attention and not involved in OFC executive functions, the 5-HT system plays a crucial role in the OFC in mediating response inhibition and reversal learning but is not integral to mPFC mediation of set-shifting and attention. These differences in monoamine regulation of these executive functions illustrate how executive functions have both specific brain region and neurochemical substrates.

The Cholinergic System: Circuitry and role in Executive Function

The mPFC and OFC both receive diffuse cholinergic input from the nucleus basalis of mynert in the basal forebrain. There are two classes of cholinergic receptors, muscarinic and nicotinic (nAChRs). The role of muscarinic receptors in executive function is not as well established as nicotinic receptor. However, disruption of muscarinic signaling via the muscarinic selective antagonist scopolamine has been shown to disrupt cognitive flexibility by disrupting set-shifting and reversal learning in rats (Chen et al. 2004). Although muscarinic receptors play a role in cognitive flexibility, there seems to be less evidence of a major role in attention. Infusion of scopolamine into the mPFC disrupted the ability of rats to complete trials but had no impact on attention measured by accuracy (Chudasama et al. 2004). In mice, systemic administration of scopolamine disrupted sustained attention but the effect on attention was confounded with the decrease in motor activity and increased response time resulting from the scopolamine (Dillon et al. 2009). In the same mouse study, administration of nicotine improved sustained attention. The nicotinic receptor subtypes will be focused on in this review as they have been implicated in cognitive and attentional processes associated with executive function (Gotti et al. 2006; Livingstone and Wonnacott 2009; Mansvelder et al. 2006; Vizi and Lendvai 1999).

Nicotinic AChRs are ligand-gated ion channels and act as excitatory receptors (Changeux and Edelstein 2005; Gotti et al. 2006; Taly et al. 2009). Nicotinic AChRs are pentameric receptors composed of a variety of 12 subunits (α2–α10 and β2–β4) that assemble in either homomeric or heteromeric receptors. β2*-containing heteromeric receptors, which are high affinity nAChRs (β2* indicates the presence of other subunits) and α7 homomeric receptors, which are low affinity nAChRs, are the most common types found in PFC (Gotti et al. 2006; Taly et al. 2009). Most nAChRs are located presynaptically and are primarily involved in regulating neurotransmitter release (Gotti et al. 2006; Livingstone and Wonnacott 2009; Mansvelder et al. 2006; Vizi and Lendvai 1999) either as autoreceptors or as heteroreceptors modulating release of DA, NE and 5-HT. In rats, the heteroreceptors in the PFC are both α7 and α4β2* nAChRs (Livingstone et al. 2009). The role of nAChRs as heteroreceptors in the PFC in conjunction with the nAChRs expressed in the VTA, LC and DR puts the cholinergic system in position to serve as a crucial modulator of the three neurotransmitter systems that are crucial for the cognitive processes mediated by the mPFC and OFC. The involvement of ACh activity in executive function has been shown by evaluating the impact of modulating nAChR function on specific cognitive processes.

There is a plethora of studies showing that modulation of nAChRs can alter attention in non-human primates and rats (Decamp et al. 2011; Demeter and Sarter 2013; Levin et al. 2006), set-shifting in rats (Alexander et al. 2012; Allison and Shoaib 2013; Brooks et al. 2012; McLean et al. 2012), reversal learning in mice (Ortega et al. 2013), and response inhibition in smokers (Rhodes et al. 2012; Wignall and de 2011). Because nicotine can either act directly on cholingeric signaling or can modulate other neurotransmitters, it is difficult to determine the neural mechanisms responsible for the effects of nicotine on executive function. Most likely, the effects of nicotine on executive function involve a complex balanced regulation of multiple neurotransmitter systems. In the following sections we will discuss the interaction of the cholinergic system with the DA, NE and 5-HT systems separately focusing on how nAChRs modulate activity in each circuit and the potential functional impact this could have on attention, set-shifting, response inhibition and reversal learning.

DA circuit in PFC: Impact of cholinergic activity on executive function

In rats, systemic administration (Nisell et al. 1996) or direct infusion (Marshall et al. 1997) of nicotine causes DA release in the mPFC. This DA release is mediated by both α7 and α4β2* nAChRs as shown by the ability of either α7- or β2*- selective agonists, infused directly into mPFC, to elicit DA release (Livingstone et al. 2009). In addition to the cholinergic modulation of DA release in PFC via nAChR heteroreceptors on dopaminergic terminals from VTA, cholinergic modulation of activity in the VTA through post-synaptic nAChRs could impact mPFC dopaminergic activity. There are functional α7 and β2* nAChRs on dopaminergic cell bodies in the VTA (Calabresi et al. 1989; Clarke and Pert 1985; Jones and Wonnacott 2004; Pidoplichko et al. 1997) and these receptors could modulate action potential firing rate, which would ultimately alter DA release at PFC synapses (Exley et al. 2011; Maskos 2008). The impact of ACh on activity in the VTA is made even more complex by the presence of α7 and α4β2* nAChRs on GABAergic interneurons in the VTA (Azam et al. 2002; Klink et al. 2001) and α7 nAChRs on glutamate

terminals (Jones and Wonnacott 2004). Nicotine effects at nAChRs on GABAergic neurons could dampen VTA dopamine release in the PFC, potentially decreasing set-shifting and attention. The end result of activation of the nAChRs expressed on other PFC and VTA neurons would be an increased DA release in PFC that would enhance set-shifting and attention.

NE circuit in PFC: Impact of cholinergic activity on executive function

There is little data on the role of nAChRs in modulation of NE release in PFC compared to the plethora of data on DA release. Gonzales et al. (1993) demonstrated that nAChR activation stimulated NE release in rat cortex and reported an interaction with NMDA receptor mediated NE release. When specifically assessing the PFC, β2* nAChR stimulated NE release was reported (Jacobs et al. 2002; Rao et al. 2003). Nicotinic AChRs also affect NE release in PFC by mediating activity in the LC, where multiple types of nAChR subunits are present. In support, the LC is excited by systemic or local administration of nicotinic agonists (Ganesh et al. 2008). In the LC, α3, α4, α5, α7, β2, β3 and β4 nAChR are expressed on the soma of neurons (Vincler and Eisenach 2003), suggesting there are a variety of nAChR stoichiometries that could be functional in the LC. Homomeric α7 nAChRs, in addition to being expressed on adrenergic neurons in the LC, are also present on GABAergic neurons in the LC (Bitner and Nikkel 2002). Activation of these α7 nAChRs receptors could dampen LC activity and decrease PFC NE release. For the NE system, all four cognitive processes would be facilitated by an overall increase in nAChR-mediated NE release in PFC.

5-HT circuit in PFC: Impact of cholinergic activity on executive function

Unlike DA and NE terminals in PFC, 5-HT terminals in PFC appear not to express nAChRs indicating that nAChRs do not modulate release of 5-HT in PFC. Pradhan et al. (2002) found no evidence of [I^{125}] epibatidine-labeled nicotinic receptors in serotonergic afferents to the cortex in rats. The lack of nAChRs on serotonin terminals in cortex was supported by later research demonstrating a failure of epibatidine to stimulate 5-HT release in PFC slices while effectively producing efflux of DA and NE (Rao et al. 2003).

Although nAChRs do not affect 5-HT release via local mechanisms in PFC, they do affect activity in the DR. Immunocytochemical studies have identified postsynaptic α7 and α4β2* nAChRs in 5-HT and non-5-HT neurons of the DR in rats (Bitner et al. 2000; Commons 2008). These postsynaptic nAChRs are functional and can increase firing rates of 5-HT neurons in DR (Galindo-Charles et al. 2008). Garduno et al. (2012) recently identified α4β2*, but not α7, autoreceptor nAChRs that increased release of ACh in the DR thereby increasing activity of serotonergic neurons in the DR. Given that 5-HT release is not directly modulated by nAChRs in PFC, nAChR-associated improvements in response inhibition and reversal learning could be due to a nAChR driven increase in firing rate of DR neurons resulting in an increase in 5-HT in PFC.

In summary, the cholinergic system operating primarily through presynaptic nAChRs could be responsible for coordinating the four sub-processes of executive function mediated by the mPFC and OFC. In the mPFC local release of DA and NE via activation of nAChR

heteroreceptors would impact set-shifting and attention while local release of NE in the OFC would modulate response inhibition and reversal learning. In addition to local effects in cortex, levels of DA, NE, and 5-HT in cortex can be modulated via nAChRs expressed in dopaminergic, noradrenergic, and serotonergic neurons in the VTA, LC and DR respectively as well as GABAergic neurons in these nuclei. The coordination of neurotransmission in these circuits in relation to executive function is an area that needs an extensive amount of additional research.

Genetic Mechanisms of Executive Function: Selective Role of Prefrontal Circuitry

The first part of this review described the role of the mPFC and OFC in set-shifting, attention, response inhibition, and reversal learning and how these processes are mediated by the DA, NE, 5-HT, and ACh transmitters systems. Additional understanding of the role each of these neurotransmitter systems plays in executive function comes from the study of the impact of genetic variation within these neurotransmitter systems on the cognitive process sub serving executive function. There are several recent reviews available that provide thorough coverage of most genome-wide association studies (Bowirrat et al. 2012; Eisenberg and Berman 2010) so the remainder of this review will focus on candidate gene studies to highlight the complexity of the neural circuitry underlying executive function.

Polymorphisms in Genes Associated with Dopamine Neurotransmission

With respect to executive function, the majority of published work focuses on the role of DA neurotransmission. There are three candidate genes involved in modulating DA activity that have variations in single nucleotide polymorphisms (SNPs) that have been associated with executive function or identified as risk genes for schizophrenia, a disorder characterized by deficits in executive function (Arguello and Gogos 2010; Barnes et al. 2011; Bowirrat et al. 2012; Eisenberg and Berman 2010): the catecholamine-O-methyltransferase (COMT) gene, the dopamine D2 receptor (DRD2), and the dopamine D4 receptor (DRD4).

COMT polymorphisms and DA function—COMT is the enzyme that degrades DA in PFC thereby regulating synaptic levels of DA (Malhotra et al. 2002). A polymorphism in COMT confers different levels of enzymatic activity to two alleles. With the COMT Val158Met (rs4680) polymorphism, the Val allele is associated with a high activity state of COMT which increases the rate of DA degradation leading of lower level of DA in PFC. The Met allele, however, produces COMT with a low activity state which slows the rate of degradation resulting in higher levels of DA. With the crucial role mPFC DA plays in set-shifting and attention, as reviewed here, these genetic-related differences in levels of mPFC DA should be associated with different performance in these executive function tasks.

Impact of COMT polymorphisms on attention—In the studies aimed at determining the impact of COMT polymorphisms on attention, a variety of tests are used to assess attention but most tests measure sustained attention. In normal adult subjects, Met/Met carriers demonstrated superior sustained attention relative to Val/Val carriers (Blasi et al. 2005; Stefanis et al. 2005). COMT genotype-associated differences in behavior are paralleled by COMT genotype-associated differences in neural activity in the mPFC during

a sustained attention task. Blasi et al. (2005) found that Val carriers who exhibited poor sustained attention had increased activity in ACC relative to Met/Met carriers who demonstrated superior sustained attention. Although most studies using normal adult subjects detect an advantage of the Met allele on sustained attention, research using younger and older subjects report conflicting data on the impact of COMT genotype on sustained attention.

In normal adolescent subjects, the impact of COMT Val158Met genotype on attention is different than adults (Wahlstrom et al. 2007). Adolescents with the Val/Met genotype exhibited the best sustained attention in comparison to the Met/Met and Val/Val genotypes (Wahlstrom et al. 2007) even though the Val/Met genotype is associated with intermediate levels of PFC DA. In contrast in adults, the Met/Met genotype, which is associated with high levels of PFC DA, is linked to optimal performance in sustained attention tasks. Lower levels of PFC DA may be required in adolescence because the PFC in not fully developed during adolescence (Spear 2000) and their circuitry may require less DA activity for optimal attention. A similar age related change is seen when older subjects are examined for association of COMT genotype with attention. Solis-Ortiz et al. (2010) found that in healthy middle-aged women, sustained attention did not vary with COMT genotype but Val/Val carriers, who have lower levels of PFC DA, showed superior selective attention (Solis-Ortiz et al. 2010). Thus, the sensitivity of the PFC DA system may change with age.

COMT polymorphisms and cognitive flexibility—The quintessential test for cognitive flexibility is the Wisconsin Card Sorting Test. Barnett et al. (2007) reported a meta-analysis of studies measuring the association of COMT Val158Met (rs4680) polymorphism with perseverative errors on the WCST in healthy individuals and schizophrenia patients. The analysis demonstrated that healthy individuals with the Met/Met genotype performed better on the WCST while no genotype difference was detected in the schizophrenia patients. Thus, healthy individuals with high levels of PFC DA exhibit an advantage in cognitive flexibility.

Unlike the lack of association of COMT Val158Met genotype and cognitive flexibility reported for schizophrenic patients (Barnett et al. 2007), a difference between COMT Val158Met genotypes has been reported for other disorders. In patients with bipolar disorder I, the COMT Val158Met Val/Val genotype was associated with improved performance on WCST in during manic episodes (Soeiro-De-Souza et al. 2012). Given that DA in PFC is elevated during manic episodes it is not unexpected that individuals carrying the alleles for the high activity type of the enzyme, which would normalize the high DA levels, demonstrated superior cognitive flexibility (Soeiro-De-Souza et al. 2012).

In addition to exploring the impact of polymorphisms in individual genes , researchers have begun assessing the impact of polymorphisms in two candidate genes. Wishart et al. (2011) genotyped healthy adults for polymorphism in their COMT, DRD2/ANKK1, brain-derived neurogrowth factor (BDNF) and Apolipoprotein E (APOE) genes. The DRD2(A1+)/ ANKK1(T allele) polymorphism is associated with decreased DRD2 receptor density in striatum, which may impact motor output in cognitive tasks. Individuals carrying COMT Met/Met showed more flexibility on the Trail Making Test compared to heterozygous or

Val/Val carriers, thus replicating the association between high levels of PFC DA and set-shifting demonstrated with the WCST. Wishart et al. (2011) also identified an interaction between COMTVal158Met genotype and the DRD2(A1+)/ANKK1(T allele) polymorphism. Individuals' carrying the COMT Val allele who were homozygous for the T allele of the DRD2/ANKK gene, had significantly reduced cognitive flexibility (Wishart et al. 2011). Thus, low levels of DA in PFC in conjunction with reduced DRD2 receptor density in striatum resulted in very low levels of cognitive flexibility. In addition to interacting with COMT, the polymorphism in DRD2/ANKK1 is independently associated with deficits in executive function.

DA receptor polymorphisms and executive functioning

DRD2 polymorphisms: DRD2 receptors are most prominently expressed in the striatum but some are expressed in the PFC as well (Markett et al. 2011). The striatal density of DRD2 receptors is determined by a single nucleotide polymorphism rs1800497 (DRD2/ANKK1 Taq Ia). Reduced striatal DRD2 density is found in individuals carrying at least one A1/T (A1+/T) allele (Ritchie and Noble 2003). The A1+ genotype has also been associated with improved cognitive flexibility (Markett et al. 2011; Stelzel et al. 2010). Relative to A1+ carriers of the DRD2/ANKK1-TaqIa polymorphism, noncarriers of the A1 allele exhibited higher striatal density of DRD2, decreased flexibility in a task-switching assay, and increased functional connectivity in dorsal frontostriatal circuits (Stelzel et al. 2010). Although this polymorphism involves striatal DA and not PFC DA specifically, changes in striatal dopamine function will impact frontostriatal circuits and alter associated behaviors.

DRD4 polymorphisms: Several different polymorphisms of the dopamine D4 (DRD4) receptor have been identified and one in particular, a 48-base pair variable number tandem repeat in exon 3, has variants associated with attentional function (DiMaio et al. 2003). The 7-repeat variant of DRD4 was shown to be half as potent in its ability to inhibit the synthesis of cyclic adenosine monophosphate (cAMP) thereby decreasing the sensitivity to DA in this variant. In healthy adults, the 7-repeat variant allele was associated with improved cognitive flexibility (Muller et al. 2007). In addition, homozygous 7-repeat carriers were more accurate in a go/no-go task compared to homozygous 4-repeat carriers (Kramer et al. 2009). These findings that expression of a less sensitive DRD4 is associated with improved cognitive flexibility and response control is consistent with the data showing that administration of DRD4 antagonist in mPFC improves set-shifting, as reviewed earlier.

Polymorphisms in Genes Associated with Noradrenergic Neurotransmission: In noradrenergic neurons, the DβH gene codes for the enzyme dopamine β-hydroxylase which catalyses the conversion of DA to NE and plays a critical role in maintaining balance of DA and NE in cortex. Polymorphisms in the DβH gene are associated with variations in DβH activity. Specifically, a C/T SNP at 1021 in the promoter region of the gene accounts for up to 50% of the variation in DβH activity (Chen et al. 2010; Tang et al. 2005; Zabetian et al. 2001). The T allele, which decreases gene transcription and slows the rate of DA conversion to NE, was associated with poor performance in a sustained attention task (Greene et al. 2009). This data is consistent with the data discussed previously demonstrating that decreases in NE in PFC results in decreased attention.

Polymorphisms in Genes Associated with Serotonergic Neurotransmission: The 1438 polymorphism in the 5-HT2A gene has been associated with expression levels of functional 5-HT2A receptors in cortex. Individuals with the A-1438A allele of the 5-HT2A receptor performed more poorly on a go/no-go task than did subjects with the G-1438G allele (Nomura et al. 2006). Although the exact influence of the 1438 polymorphism on the 5-HT2A receptor is unknown, the reduced response inhibition could be due to a decreased expression of 5-HT2A receptors on pyramidal neurons in cortex. This would be consistent with fact that activation of excitatory 5-HT2A receptors in OFC is associated with improved response inhibition.

Two polymorphisms in the serotonin transporter (5HTTLPR) have been associated with improved cognitive flexibility as measured by reversal learning in rhesus macaques. Izquierdo et al. (2007) reported that rhesus monkeys carrying 2 copies of the short allele of the rhesus 5-HTT gene-linked polymorphic region showed significantly reduced cognitive flexibility as measured in object discrimination reversal learning. Similarly, a functional genetic variation at the serotonin transporter 30 untranslated region, independent of 5HTTLPR, was associated with errors in reversal learning (Vallender et al. 2009). The polymorphism comprising haplotype (T1970, G1991, and T2327 (T:G:T)) was associated with lower levels of gene expression and monkeys with the T:G:T haplotype made fewer errors in reversal learning than the C:C:C haplotype. If this polymorphism in the serotonin transporter results in decreased reuptake of serotonin, the reversal learning results are consistent with other results showing that increased 5-HT activity in OFC is associated with superior reversal learning.

A Polymorphism in a Gene Associated with Cholinergic Neurotransmission: The CHRNA4 gene codes for the α4 subunit of the α4β2 nAChRs. A SNP (rs1044396) has been identified that involves a C to T substitution (Steinlein et al. 1997). This SNP may be associated with altered attention. In an extensive review of the literature, Greenwood et al. (2012) concluded that the T allele is associated with better attention and higher cortical activity. This conclusion is consistent with the reviewed literature showing that nicotine can improve attention.

Conclusions: Executive function, as reviewed, is not a singular cognitive process but instead a collective of multiple complex cognitive processes that regulate higher mental function. Whereas these processes can work together to regulate cognition, they are differentially altered by monoamines and cholinergic afferents into the underlying cortical substrates and by polymorphisms associated with these neurotransmitter systems. Attention largely involves the mPFC and is increased by NE, DA, and ACh in healthy individuals. Polymorphisms in genes associated with COMTVal158Met, DRD2/ANKK1, DRD4, DβH, and CHRNA4 alter attention. Cognitive flexibility as measured by set-shifting involves mPFC and increases in DA, NE, and ACh in healthy individuals while polymorphisms in genes associated with COMTVal158Met, DRD2/ANKK1, and DRD4 alter cognitive flexibility. Interestingly, while reversal learning is also a measure of cognitive flexibility, it involves different neural substrates than set-shifting. Specifically, NE, 5-HT, and ACh increases in OFC improve reversal learning. Two different polymorphisms in the serotonin

transporter (5HTTLPR) affect reversal learning. Finally, response inhibition involves NE, 5-HT, and ACh activity in OFC with increases in neurotransmitter levels improving response inhibition. The 1438 polymorphism in the 5-HT2A gene has been associated with altered response inhibition. Understanding the neural substrates of executive function and how these processes are altered with changes in neurotransmitter signaling and gene expression in healthy individuals and those with cognitive deficits will advance treatment of mental illnesses.

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Highlights

- Executive function is a collective of multiple complex cognitive processes that regulate higher mental function
- Executive function associated processes are differentially altered by monoamines and cholinergic afferents into the underlying cortical substrates
- Polymorphisms associated with monoamines and acetylcholine impact executive function