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REVIEW

A neurochemical yin and yang: does serotonin activate and norepinephrine deactivate the prefrontal cortex?

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Abstract
Introduction The prefrontal cortex (PFC) receives serotonergic input from the dorsal raphe nucleus of the brainstem, as well as noradrenergic input from another brainstem nucleus, the locus coeruleus. A large number of studies have shown that these two neurotransmitter systems, and drugs that affect them, modulate the functional properties of the PFC in both humans and animal models.
Results Here I examine the hypothesis that serotonin (5-HT) plays a general role in activating the PFC, whereas norepinephrine (NE) plays a general role in deactivating this brain region. In this manner, the two neurotransmitter systems may have opposing effects on PFC-influenced behavior. To assess this hypothesis, three primary lines of evidence are examined comprising the effects of 5-HT and NE on impulsivity, cognitive flexibility, and working memory.
Discussion While all of the existing data do not unequivocally support the activation/deactivation hypothesis, there is a large body of support for it.

Keywords Executive function · Impulsivity · Cognitive flexibility · Reversal learning · Working memory · Fluoxetine · Clonidine · Propranolol · Guanfacine

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Introduction

The prefrontal cortex (PFC) has undergone marked expansion and changes in folding through the course of primate evolution (Rilling and Insel 1999; Semendeferi et al. 2001). The conventional wisdom may be that during mammalian and particularly primate evolution, there has been intense selective pressure to produce a more fully developed PFC, leading to greater cognitive capacity that could result in increased survival and enhanced reproductive success. However, if excessive functional activation of PFC actually produces evolutionarily unfavorable traits, such as marked behavioral inhibition, then a large or overly active PFC may in fact not be selected for, at least not in all individuals. This paper puts forward the hypothesis that in order to produce a broad range of variation in personality or specialized behavior across individuals within primate species, endogenous neurochemical activation or deactivation of PFC has evolved within the population of primates and possibly within most or all animals that have a PFC or homologous brain region. A large degree of variation in PFC activation across individuals of a given species may allow particular individuals to better fill specialized behavioral niches within that species. Likewise, some degree of variability in the size of PFC also may have been selected for within species.

Phineas Gage, the American railroad worker who in the 1800s accidentally sustained what appears to have been a large-scale lesion of the PFC, provides a famous example of how damage to this brain structure can result in profound changes in personality and behavior (Harlow 1868). Upon first consideration it would appear that Gage's reportedly irresponsible post-lesion behavior and possibly frequent changes in place of residence (associated with traveling around and displaying the tamping iron that damaged his

brain for money, as well as moving to and working in Chile) greatly impaired his ability to function (Harlow 1868). While his capacity to function in the conventional sense may indeed have been diminished, one can speculate that irresponsible behavior and/or frequent changes in place of residence may be, from an evolutionary perspective, selected for at least in a subset of individuals, especially when combined with sexual promiscuity (particularly in males). Such a person may produce a large number of offspring while not expending significant resources to help raise them. Gage's case is of interest for our purposes since we may speculate that lesioning of PFC is a coarse form of "deactivation" of this brain region, and Gage may in some ways represent someone with an underfunctioning or undersized PFC, where his behavior may nonetheless have evolutionary advantages. If so, and if genetically diminished prefrontal activation exists in some humans (or members of other species), such genes and corresponding phenotypes could be retained in the population over time. Persons with prefrontal lobotomies, where this procedure was fairly common in the United States decades ago, also represent cases of large-scale lesioning of PFC (El-Hai 2007). However, these persons may not provide much insight into the topic at hand because they typically were suffering from severe mental illness (El-Hai 2007).

The rest of the paper focuses on the hypothesis that 5-HT and NE tend to, respectively, activate and deactivate the PFC, both in humans and other species, not limited to primates. Most of the data reviewed comprise the following three lines of evidence, which are standard components of PFC "executive" function: impulsivity, cognitive flexibility (with particular focus on reversal learning), and working memory (Dalley et al. 2004; Holmes and Wellman 2009). The focus is on pharmacological studies that manipulated the synaptic concentration of the two transmitters rather than a detailed review of the effects of receptor subtype specific drugs, although some data will be provided on the adrenoceptor blocking drugs, propranolol (a nonselective beta blocker) and prazosin (an alpha1 blocker), and a few other subtype specific drugs.

Impulsivity and 5-HT

Impulsivity refers to premature, unduly risky, poorly conceived actions; pathological impulsivity includes deficits in attention and lack of reflection and/or insensitivity to the consequences of one's actions (Crews and Boettiger 2009). Impulse control is considered an executive function that is mediated, at least in part, by the PFC (Crews and Boettiger 2009), and it has been studied both in humans and animal models, including rodents (Dalley et al. 2008). A recent review suggests that 5-HT is positively associated with response inhibition (Cools et al. 2008).

A number of studies have suggested a link between reduced 5-HT transmission and increased impulsivity. A lower cerebrospinal fluid (CSF) concentration of the 5-HT metabolite, 5-HIAA, has been associated with a greater degree of impulsivity (and suicidality) (Roggenbach et al. 2002). In a group of drug-free suicide attempters and control subjects, impulsive suicide attempters had lower plasma 5-HIAA than non-impulsive attempters or control subjects (Spreux-Varoquaux et al. 2001). There is evidence that impulsive violent offenders who tend to behave aggressively while intoxicated on alcohol have low brain 5-HT turnover (Virkkunen et al. 1995). A study of violent offenders found that those who impulsively committed their crimes had lower CSF 5-HIAA than those who premeditated their acts (Linnoila et al. 1983). In a study of substance abusers, administration of the 5-HT agonist fenfluramine produced a greater plasma prolactin response in subjects with a higher degree of impulsivity (Fishbein et al. 1989). On the other hand, in a study of healthy volunteers who exhibited differing degrees of impulsivity, prolactin responses to fenfluramine were lower in persons showing a high degree of impulsivity (Evans et al. 2000). In male vervet monkeys, CSF 5-HIAA was inversely related to a measure of social impulsivity, and treatment with fluoxetine decreased such impulsivity (Fairbanks et al. 2001).

Pharmacological studies have shown that chronic but not acute administration of selective serotonin reuptake inhibitors (SSRIs: fluoxetine, citalopram, paroxetine) increased the ability of pigeons to delay receiving reinforcement, which corresponds to a decrease in impulsivity (Wolff and Leander 2002). In rats trained to press a lever a fixed number of consecutive times before pressing a second lever for reinforcement, the 5-HT lowering drug PCPA produced lever pressing behavior consistent with increased impulsivity (Evenden 1998). Rats that have the 5-HT transporter genetically deleted, where this may produce increased synaptic levels of 5-HT, display reduced aggression and increased inhibitory control (Homberg et al. 2007). The knockout mouse that lacks the 5-HT1B receptor (where these mice have impaired autoinhibition of 5-HT release, Rutz et al. 2006) shows increased impulsive aggression (Brunner and Hen 1997; Scearce-Levie et al. 1999). Another study, which used an operant differential-reinforcement-of-low-rates procedure, found that 5-HT1B but not 5-HT1A knockout mice exhibit increased impulsivity (Pattij et al. 2003). In rodents, 5-HT2A and 5-HT2C antagonist drugs appear to have opposing effects on impulsivity as measured by the 5-choice serial reaction time task (Winstanley et al. 2004; Fletcher et al. 2007), although this functional opposition may be mediated by

the nucleus accumbens rather than medial PFC (Robinson et al. 2008a).

These data on 5-HT tend to support the hypothesis that decreased serotonergic transmission is associated with increased impulsivity, and increased transmission with decreased impulsivity, extending to both human and animal studies and supporting the 5-HT/activation hypothesis. However, two studies showed opposite results for the relationship between fenfluramine drug challenge and impulsivity (Fishbein et al. 1989; Evans et al. 2000). Another caveat is that some of these data comprise the 5-HT metabolite, 5-HIAA (Roggenbach et al. 2002; Spreux-Varoquaux et al. 2001; Linnoila et al. 1983; Fairbanks et al. 2001), where the relationship with brain 5-HT is unclear, although a parsimonious hypothesis is that 5-HT and 5-HIAA covary in concentration. It is also unclear whether deletion of the 5-HT1A and 5-HT1B receptor subtypes decreases or increases serotonergic transmission (Brunner and Hen 1997; Scearce-Levie et al. 1999; Pattij et al. 2003), partly because these receptor subtypes may partially function as inhibitory autoreceptors rather than just post-synaptic receptors (Rutz et al. 2006).

Impulsivity and NE

NE, like 5-HT, appears to play a role in impulsivity. In general, some human studies indicate that increasing NE correlates positively with impulsive aggression, whereas other studies demonstrate the opposite relationship (Oquendo and Mann 2000). In a study of the relationship between variation in the promoter region of the adrenergic2A receptor gene and impulsivity in normal subjects, there were genotype associations with impulsivity scores in the Multidimensional Personality Questionnaire (Comings et al. 2000). The spontaneously hypertensive rat, which exhibits impulsivity relative to normotensive rats, shows diminished autoreceptor-mediated inhibition of NE release in the PFC (Russell 2002). In the coloboma mouse model of ADHD, reduction of NE with the drug DSP-4 restored latent inhibition but did not decrease impulsivity (Bruno et al. 2007). In grivet monkeys living in their natural habitat, a measure of impulsivity based on entering baited traps a second time after the animal had already been captured, was positively related to lower levels of CSF MHPG, an NE metabolite (Fairbanks et al. 1999).

NE reuptake inhibiting drugs such as desipramine, reboxetine, and atomoxetine, which boost the level of synaptic NE (but may also boost the level of dopamine in the PFC; see Discussion), also appear to have effects on impulsivity. In a placebo-controlled study of adult ADHD, chronic desipramine produced a decrease in impulsivity, hyperactivity, and inattentiveness (Wilens et al. 1996). In an open-label trial of reboxetine in children with hyperkinetic conduct disorder, there were decreases in associated symptoms such as impulsivity and aggressiveness (Mozes et al. 2005). In a long-term open-label study of atomoxetine in adult ADHD, where subjects had been followed for up to 97 weeks, atomoxetine use was associated with reduction of symptoms (Adler et al. 2005). In a double-blind, placebo-controlled study of adult ADHD, acute atomoxetine improved inhibitory control as measured by shorter stop-signal reaction times (Chamberlain et al. 2007a). In a study of 60 healthy males, response inhibition was enhanced by atomoxetine but unaffected by citalopram, whereas probabilistic learning was unaffected by atomoxetine but impaired by citalopram, suggesting dissociable effects of NE and 5-HT in these tasks (Chamberlain et al. 2006).

In a delayed reward task in rats, desipramine had no effect on impulsivity, the alpha2 agonist clonidine (which decreases synaptic PFC NE when infused in the locus coeruleus (van Gaalen et al. 1997) but activates postsynaptic alpha2 receptors) increased impulsivity, and the alpha1 agonist phenylephrine had no effect (van Gaalen et al. 2006). In a task in which rats were trained to delay choosing between two levers for food reward, desipramine but not amphetamine (which releases dopamine and other neuromodulators) reduced impulsive responding (Evenden 1999). Atomoxetine reduced impulsivity in three distinct measures in the rat: stop-signal reaction time performance, delay discounting of reward, and the five-choice serial reaction time task (Robinson et al. 2008b). Acute administration of atomoxetine in rats performing the five-choice serial reaction time task produced a reduction in impulsivity, and low dose methylphenidate improved overall attention (Navarra et al. 2008). Atomoxetine also improved performance on the stop-signal paradigm in rats, whereas citalopram and the dopamine boosting drug, GBR-12909, had mild, distinct effects (Bari et al. 2009).

Experiments using a variety of other noradrenergic drugs also suggest that NE has an effect on impulsivity. In a double-blind, placebo-controlled study of children and adults with Tourette syndrome, a 12-week trial of clonidine produced a reduction in impulsivity and other behavioral symptoms related to this disorder (Leckman et al. 1991). In persons with ADHD, clonidine is effective at reducing hyperactivity and impulsivity (Pityaratstian 2005). In a double-blind, placebo-controlled, 16-week study of children with comorbid ADHD and a chronic tic disorder, clonidine combined with methylphenidate produced the greatest relief of symptoms relative to placebo and each of these drugs given alone (Tourette's Syndrome Study Group 2002). In this study, clonidine was most effective for impulsivity and hyperactivity, whereas methylphenidate was most effective for inattention (Tourette's Syndrome

Study Group 2002). In a double-blind, randomized study that compared clonidine with carbamazepine in children with ADHD over a period of two years, clonidine was effective in reducing hyperactivity and impulsivity relative to carbamazepine (Nair and Mahadevan 2009). In healthy subjects, the noradrenergic alpha2 antagonist drug yohimbine, which increases synaptic NE release but blocks postsynaptic alpha2 receptors, acutely produced dose-dependent increases in impulsive errors in the immediate and delayed memory tasks (Swann et al. 2005).

In rats performing a 5-choice serial reaction time task, propranolol abolished methylphenidate-induced impulsivity, prazosin partially attenuated such impulsivity and cortical noradrenergic depletion did not alter this impulsivity (Milstein et al. 2008). In another study of this task in rats, the premature responding induced by the 5-HT2A/2C agonist DOI was antagonized by prazosin (Koskinen et al. 2003).

How these data on NE and impulsivity relate to the PFC NE/deactivation hypothesis depends largely on how the studies of the NE reuptake inhibiting drugs and alpha2 agonists and antagonists are interpreted. The NE reuptake inhibitors appear to decrease impulsivity (Wilens et al. 1996; Mozes et al. 2005; Adler et al. 2005; Chamberlain et al. 2007a; Evenden 1999; Robinson et al. 2008b; Navarra et al. 2008; Bari et al. 2009), thereby opposing the hypothesis, but these drugs also boost PFC dopamine (Tanda et al. 1994; Page and Lucki 2002; Bymaster et al. 2002), which may be the factor that is activating PFC. The alpha2 agonist clonidine tends to decrease impulsivity (Leckman et al. 1991; Pityaratstian 2005; Tourette's Syndrome Study Group 2002; Nair and Mahadevan 2009), which would be consistent with the NE/deactivation hypothesis as long as the principal effect of the drug is decreasing NE release (van Gaalen et al. 1997) rather than increasing neurotransmission by agonizing postsynaptic alpha2 receptors. Two studies on the adrenoceptor blocking drugs, propranolol, and prazosin (Milstein et al. 2008; Koskinen et al. 2003), are consistent with the NE/deactivation hypothesis.

Cognitive flexibility and 5-HT

5-HT also appears to play a role in the cognitive flexibility, which can be defined as the ability to adjust behavior to changes in the environment or task conditions (Evers et al. 2007). This section summarizes some of these data, with a focus on reversal learning. A caveat is that not all forms of cognitive flexibility, such as reversal learning and attentional set shifting, may be modulated in the same direction by 5-HT and NE, and the effects of these neuromodulators may be independent rather than opposed (Robbins and Roberts 2007). In a study of acute tryptophan depletion (which reduces brain 5-HT) in healthy volunteers, this manipulation produced slowed responding in a visual discrimination and reversal learning task (Murphy et al. 2002). In a double-blind, placebo-controlled study of 60 healthy male volunteers, acute buspirone failed to affect measures of impulsivity or cognitive flexibility (Chamberlain et al. 2007b).

In a study using rats, acute tryptophan depletion did not affect several measures of spatial reversal learning, suggesting that this form of reversal learning, in contrast to visual reversal learning, may not depend on 5-HT (van der Plasse and Feenstra 2008). In rats performing an attentional set-shifting task, 5-HT depletion with the drug PCPA produced a deficit in reversal learning, and chronic intermittent cold stress did so as well, where the latter effect was attenuated by acute administration of citalopram (Lapiz-Bluhm et al. 2009). In rats performing an operant reversal learning task, the NMDA receptor antagonist PCP given subchronically produced deficits in reversal that were antagonized by buspirone (McLean et al. 2009). In marmosets performing a serial discrimination reversal paradigm, selective 5-HT depletion in the PFC produced perseverative responding to the previously rewarded stimulus upon reversal (Clarke et al. 2004). Marmosets with selective PFC 5-HT lesions were impaired in reversal learning but not extradimensional set shifting (Clarke et al. 2005). Rhesus monkeys with two copies of the short allele of the rhesus 5-HTT (i.e., the 5-HT transporter) gene-linked polymorphic region (rh5-HTTLPR) showed reduced cognitive flexibility on two tasks: object discrimination reversal learning and instrumental extinction (Izquierdo et al. 2007). Genetic variation at the 5-HTT 3′ untranslated region, independent of rh5-HTTLPR, also affects performance in object discrimination reversal learning in rhesus monkeys (Vallender et al. 2009).

These data on 5-HT and cognitive flexibility largely comprise studies of 5-HT depletion (via tryptophan and possibly via buspirone), with more studies suggesting that depletion impairs flexibility (Murphy et al. 2002; Lapiz-Bluhm et al. 2009; Clarke et al. 2004, 2005) rather than improves it (McLean et al. 2009), or has no effect (Chamberlain et al. 2007b; van der Plasse and Feenstra 2008). Two rhesus monkey studies at least support a role for 5-HT in cognitive flexibility (Izquierdo et al. 2007; Vallender et al. 2009). In sum, these studies tend to support the hypothesis that 5-HT activates the PFC.

Cognitive flexibility and NE

NE also appears to play a role in cognitive flexibility, including reversal learning. In a study of 18 normal subjects performing an anagram task that relied heavily upon cognitive flexibility, subjects given acute propranolol were able to solve the problems more quickly than subjects given

ephedrine (Beversdorf et al. 1999). Propranolol, which is a peripheral and central beta blocker, also produced shorter anagram solution latencies than nadolol, a peripheral beta blocker, implicating central beta receptors in this behavioral effect (Beversdorf et al. 2002). In an additional study by Beversdorf et al., anagram solution times were significantly faster after propranolol, but not after the benzodiazepine lorazepam, relative to placebo, suggesting that the propranolol effect is not a nonspecific anxiolytic effect but is specific to the adrenergic system (Silver et al. 2004). However, this group of researchers found no significant effect of clonidine on cognitive flexibility in a study of healthy subjects (Choi et al. 2006). In a more recent study, these researchers found that propranolol may produce greater improvement in cognitive flexibility during solution of more difficult anagram problems (Campbell et al. 2008).

In rats with lesions of the dorsal noradrenergic ascending bundle, which depleted medial PFC NE by about 70%, there was impairment of attentional set shifting but not reversal learning (Tait et al. 2007). In a study of extradimensional set shifting in the rat, chronic administration of the antidepressant desipramine enhanced cognitive flexibility (Lapiz et al. 2007). In rats and vervet monkeys performing, respectively, a four-position discrimination task or a three-choice visual discrimination task, drugs that inhibit the NE transporter (methylphenidate, atomoxetine, and desipramine) improved reversal performance (Seu et al. 2009). In rats performing a water-maze task, propranolol, when combined with the cholinergic antagonist scopolamine, impaired reversal learning (Saber and Cain 2003). In marmosets performing visual discrimination learning tasks in a Wisconsin General Test Apparatus, the drug aceperone, which increases the release of NE (Braestrup and Nielsen 1976), produced deficits in new and repeated reversal learning (Ridley et al. 1981). In aged rhesus monkeys performing a visual object discrimination task, guanfacine produced improvement in reversal learning at high but not low doses (Steere and Arnsten 1997). In cynomolgus monkeys performing a reversal learning task, pretreatment with citalopram or desipramine, but not methylphenidate, blocked MDMA-induced task impairment (Verrico et al. 2008).

These results on NE and cognitive flexibility provide inconsistent support for the NE/deactivation hypothesis. Human studies on the central beta blocker, propranolol, support the hypothesis (Beversdorf et al. 1999, 2002; Silver et al. 2004; Campbell et al. 2008). However, several animal studies showed that NE boosting drugs such as desipramine, methylphenidate and atomoxetine improve cognitive flexibility (Lapiz et al. 2007; Seu et al. 2009; Verrico et al. 2008). As with the impulsivity studies, these drugs could be boosting dopamine and thereby activating the PFC, which would still be consistent with the NE/deactivation hypothesis. The alpha2 agonist guanfacine improved reversal learning in aged monkeys (Steere and Arnsten 1997), and the direction of this effect on NE signaling is open to interpretation, as discussed for impulsivity. The other studies provide mixed results for the deactivation hypothesis (Tait et al. 2007; Saber and Cain 2003; Ridley et al. 1981).

Working memory and 5-HT

Working memory can be defined as a multi-component system that holds and manipulates information in short-term memory, subject to temporal decay and chunk capacity limits (Cowan 2008). A number of studies indicate that 5-HT plays a role in working memory, although not all studies support this hypothesis. In healthy adults who had their 5-HT boosted through dietary tryptophan loading, or reduced through tryptophan depletion, behavioral testing revealed impairment in working memory for verbal and affective stimuli following tryptophan loading versus depletion (Luciana et al. 2001). In a double-blind, placebo-controlled study that included persons with Alzheimer's disease and healthy elderly subjects, acute tryptophan depletion produced impairment in working memory in both groups of people (Porter et al. 2003). In healthy female volunteers, tryptophan depletion impaired declarative memory consolidation, whereas tyrosine and phenylalanine depletion (to reduce NE and dopamine) impaired spatial working memory (Harrison et al. 2004). In an fMRI study of healthy right-handed volunteers, acute tryptophan depletion attenuated activation of the right superior frontal gyrus during a 2-back verbal working memory task (Allen et al. 2006). In a study of normal human subjects performing a visuospatial working memory task, the 5-HT agonist fenfluramine impaired task performance (Luciana et al. 1998).

In a double-blind, placebo-controlled study of persons with schizophrenia or schizoaffective disorder, buspirone had no significant effect on performance of an n-back spatial working memory task (Piskulic et al. 2009). In another double-blind, placebo-controlled study of persons with schizophrenia, buspirone added to an atypical antipsychotic drug regimen had no significant effect on verbal working memory (Sumiyoshi et al. 2007). In rats, buspirone (but not alprazolam) impaired performance of a three-choice working memory water escape task (Bass et al. 1992). In another rat study, buspirone had no significant effect on working memory in a delayed spontaneous alternation task, whereas diazepam produced impairment in working memory (Wada and Fukuda 1992).

In a placebo-controlled study of persons with major depression, chronic administration of amitriptyline (a tricyclic antidepressant) or fluoxetine resulted in clinical improvement in both drug groups, but persons receiving amitriptyline did not perform as well on an auditory verbal

learning test of working memory (Richardson et al. 1994). In a 3-month open-label study of persons with major depression who took an SSRI, antidepressant responders outperformed nonresponders across a number of cognitive domains, including working memory function (Gorlyn et al. 2008).

In a rat study, lesions of serotonergic neurons with the toxin 5,7-dihydroxytryptamine, when combined with cholinergic lesions, impaired spatial working memory in the T maze and Morris water maze (Lehmann et al. 2000). In the rat, lesioning the 5-HT system with 5,7-dihydroxytryptamine impaired acquisition but not later performance of a nonspatial working memory task, non-match-to-sample object recognition in the Y-maze (Cassaday et al. 2003). In another study of 5,7-dihydroxytryptamine in the rat, this serotonergic lesion decreased spontaneous alternation in a Y-maze task and impaired working memory in a radial eight arm maze task (Hritcu et al. 2007). Mice with deletion of the 5-HT1B receptor subtype exhibited impairment in a delayed spatial matching-to-sample working memory task in a radial-arm water maze (Buhot et al. 2003).

In rats performing a water-maze task, combined treatment with the cholinergic drug atropine and the 5-HT depleting drug PCPA produced impairment in working memory, although PCPA had no effect when given alone (Richter-Levin and Segal 1989). In another study of rats, PCPA or the 5-HT blocker methysergide did not appear to have an important mnemonic effect in a delayed non-matching to position task (Jakala et al. 1993). Rats given the tricyclic antidepressant, imipramine (which may principally boost NE (Jordan et al. 1994)), had impaired spatial working memory in a radial-arm maze task, whereas administration of the SSRI, paroxetine, did not alter performance (Naudon et al. 2007). In a study of rats performing a multiple fixed-ratio schedule of lever pressing for food reinforcement, fluoxetine reduced lever pressing rate but did not affect an estimate of working memory capacity (Sanabria et al. 2008).

The above data tend to support the hypothesis that 5-HT transmission positively correlates with working memory capacity, thereby supporting the 5-HT/activation hypothesis. 5-HT reduction via tryptophan depletion impaired working memory (Porter et al. 2003) or attenuated frontal cortical activation (Allen et al. 2006) in humans. However, one study found that tryptophan *loading* versus depletion impaired working memory (Luciana et al. 2001). One rat study showed working memory impairment with the 5-HT reducing drug, buspirone (Bass et al. 1992). Persons recovering from major depression showed improvements in working memory on an SSRI (Richardson et al. 1994; Gorlyn et al. 2008), but this could be related to clinical improvement. In rats, serotonergic lesions produced impairment in spatial working memory (Lehmann et al. 2000; Hritcu et al. 2007), and 5-HT depletion with PCPA also produced working memory impairment (Richter-Levin and Segal 1989). The rest of the above studies were largely negative results for working memory alteration.

Working memory and NE

NE, like 5-HT, appears to play a role in working memory. In a double-blind, placebo-controlled study of healthy male volunteers, reboxetine improved working memory performance in a temporal information processing task (Rammsayer et al. 2001). In healthy volunteers, acute propranolol increased reaction times in a numeric working memory task, whereas atenolol (a peripheral beta blocker) had no such effect (Muller et al. 2005). In human subjects, guanfacine improved performance of a spatial working memory task, whereas clonidine dose-dependently disrupted performance (Jakala et al. 1999).

In a study of aged rhesus monkeys with known memory impairments, the alpha2 agonist clonidine improved spatial working memory in all 13 monkeys tested, and the effect was blocked by alpha2 but not alpha1 antagonists (Arnsten and Goldman-Rakic 1987). In nine aged rhesus monkeys performing a variable delay, spatial delayed response task, clonidine impaired memory and produced sedation at low doses while high doses improved memory, whereas guanfacine improved memory at low doses while impairing memory and producing sedation at higher doses (Arnsten et al. 1988). In aged rhesus monkeys performing a delayed non-match-to-sample task, clonidine produced a triphasic dose/response curve, with impairment at both very low and high doses and modest improvement in the middle dose range (Arnsten and Goldman-Rakic 1990).

Administration of low doses of clonidine to chronically reserpine-treated monkeys (where reserpine depletes catecholamines) restored performance on a delayed response spatial working memory task, suggesting that the beneficial effect of clonidine was achieved through activation of postsynaptic alpha2 receptors (Cai et al. 1993). Very low doses of the alpha2 antagonist, yohimbine, improved spatial working memory in a subset of tested monkeys, and this beneficial effect (and the beneficial effect of clonidine) was blocked by the alpha2 antagonist, SKF104078 (Arnsten and Cai 1993). PFC infusion of phenylephrine in the monkey impaired performance of a delayed response task, whereas infusion of the alpha2 agonist guanfacine improved performance (Mao et al. 1999). In normal young macaque monkeys, clonidine but not the benzodiazepine diazepam, improved spatial working memory during a delayed response task (Franowicz and Arnsten 1999). In a SPECT brain imaging study of monkeys, guanfacine improved performance of a spatial working memory task, and

increased regional cerebral blood flow in dorsolateral PFC during the task (Avery et al. 2000). In the monkey, systemically administered clonidine (and clonidine iontophoretically applied to the PFC) enhanced spatial working memory-related neural activity in the PFC, and iontophoretically applied yohimbine tended to suppress such neural activity or antagonize the effects of clonidine (Li et al. 1999). Low doses of the alpha1 agonist, cirazoline, impaired spatial working memory in a variable delayed response task in aged rhesus monkeys, and the effect was blocked by the alpha1 antagonist, prazosin (Arnsten and Jentsch 1997). The beta1 antagonist, betaxolol, produced a dose-related improvement in working memory performance following either direct PFC infusion in rats or systemic administration in monkeys (Ramos et al. 2005). The beta2 *agonist*, clenbuterol, also moderately improved working performance in a subset of both young and aged rats and monkeys that exhibited working memory impairment at baseline (Ramos et al. 2008). In rats and monkeys, pharmacological treatments that increase cAMP-mediated signaling block the beneficial effects of guanfacine on working memory (Ramos et al. 2006). Further, alpha2A receptor stimulation may strengthen working memory through inhibition of cAMP signaling by closing hyperpolarization-activated cyclic nucleotide-gated (HCN) channels (Wang et al. 2007).

Lesions of the rat locus coeruleus impaired spatial working memory in a Greek cross version of the Morris water maze (Compton et al. 1995). In rats with 6-hydroxydopamine lesions of medial PFC (and resulting deficits in NE and dopamine in this brain region) performing a T maze delayed response task, chronic desipramine impaired performance of control rats but attenuated deficits in lesioned rats (Clinton et al. 2006). Reversible lidocaine-based bilateral inactivation of the locus coeruleus in the rat significantly impaired working memory in the Morris water maze (Khakpour-Taleghani et al. 2009). In rats performing a radial-arm maze working memory task, scopolamine, a muscarinic antagonist, impaired task performance of animals depleted of NE with 6-hydroxydopamine more than non-depleted animals (Decker and Gallagher 1987). Desipramine administered systemically to rats in single daily doses across 15 days produced deficits in long-term visuospatial memory in the radial-arm maze, without inducing changes in working memory (Burgos et al. 2005). In rats performing a delayed alternation task in a T maze, a test of spatial working memory, PFC NE, and dopamine dialysate levels phasically increased when the animals performed the task correctly (Rossetti and Carboni 2005). Infusion of phenylephrine into the PFC of rats markedly impaired performance of a spatial working memory task, delayed alternation (Arnsten et al. 1999). In rats performing a delayed non-matching to position working memory task, prazosin lengthened the latency for correct responses, and the authors conclude that alpha1 receptors do not play an important role in spatial working memory but may affect motor activity and motivation (Puumala and Sirvio 1997). In mice, the improvement in working memory produced by guanfacine may be mediated by the alpha2A receptor subtype rather than alpha2C (Franowicz et al. 2002).

The above working memory data provide mixed support for the NE/deactivation hypothesis, and as for impulsivity and cognitive flexibility, the conclusion depends strongly on the interpretation of the results of the NE boosting drugs and especially the alpha2 drugs. Reboxetine improved working memory in humans (Rammsayer et al. 2001), and desipramine showed mixed effects in rats (Clinton et al. 2006; Burgos et al. 2005). In various species, clonidine and guanfacine also produced mixed results on working memory, but they more frequently improved (Jakala et al. 1999; Arnsten and Goldman-Rakic 1987; Cai et al. 1993; Arnsten and Cai 1993; Mao et al. 1999; Franowicz and Arnsten 1999; Avery et al. 2000) than impaired it (Jakala et al. 1999), while showing both effects at various doses in some studies (Arnsten et al. 1988; Arnsten and Goldman-Rakic 1990). The alpha2 antagonist, yohimbine, improved spatial working memory in monkeys (Arnsten and Cai 1993). If alpha2 agonists are principally reducing noradrenergic transmission, then these data tend to support the NE/deactivation hypothesis. Results from various adrenoceptor subtype selective drugs, such as propranolol, prazosin, phenylephrine, cirazoline, betaxolol, and clenbuterol tend to support the NE/deactivation hypothesis (Arnsten and Jentsch 1997; Mao et al. 1999; Arnsten et al. 1999; Ramos et al. 2005) rather than oppose it (Muller et al. 2005; Ramos et al. 2008).

Discussion

While all of the data reviewed above certainly do not unequivocally support the activation/deactivation hypothesis, on the whole they tend to support it. There are a few points which, depending on how they are interpreted, strongly affect the merits of the hypothesis. As described above, one point concerns the data on the alpha2 agonists, clonidine and guanfacine, as well as data on alpha2 antagonists such as yohimbine. Many of these data suggest improvements in impulsivity and working memory with alpha2 agonists, suggesting activation of PFC by these drugs. The parsimonious interpretation may be that alpha2 agonists (opposite for alpha2 antagonists) are producing a net decrease in NE transmission, since they lower the synaptic concentration of NE (van Gaalen et al. 1997) for all adrenoceptors but only agonize one subtype of postsyn-

aptic adrenoceptor, alpha2 (possibly alpha2A in particular, Franowicz et al. 2002). Moreover, postsynaptic alpha2 receptors may be functionally opposed to other adrenoceptors, especially considering that presynaptic alpha2 receptors are "inhibitory" autoreceptors. This type of reasoning suggests that the alpha2 drug data tend to support the hypothesis that NE deactivates PFC.

Another critical point raised by the above data is that NE boosting drugs (tricyclic antidepressants, reboxetine, and atomoxetine) may activate PFC-mediated executive functions, which would work against the NE/deactivation hypothesis. However, these drugs boost PFC dopamine in rodent microdialysis studies (Tanda et al. 1994; Page and Lucki 2002; Bymaster et al. 2002), so dopamine may be the principal means through which they achieve their effects on PFC-modulated behavior. If so, the data on these drugs may still tend to be consistent with NE producing deactivation. Arguing against this simple hypothesis, however, are some of the above findings that dopamine boosting drugs do not have the same effects as NE boosting drugs (Evenden 1999; Robinson et al. 2008b; Navarra et al. 2008; Verrico et al. 2008; Bari et al. 2009).

A few of the above studies provide direct evidence for the activation/deactivation hypothesis based on brain imaging (Allen et al. 2006; Avery et al. 2000) or neural recording (Li et al. 1999) from PFC in the context of 5-HT and NE manipulation, strengthening the hypothesis.

One critical point is that even if the hypothesis, or a variant of it, is correct, 5-HT and NE may very likely not be the sole determinants of PFC activation. Other genetic or environmental factors may also play an important role, perhaps encompassing a larger effect than these or other neuromodulators. Another point is that phasic versus tonic 5-HT and NE may differentially affect PFC activation (Florin-Lechner et al. 1996; Aston-Jones et al. 1999; Rossetti and Carboni 2005). Phasic refers to rapid, acute changes in transmitter release, whereas tonic refers to relatively steady, baseline release of the transmitter. Based on a computational model, phasic NE release by the locus coeruleus may promote focused or selective attention, whereas tonic release may produce a state of high behavioral flexibility or scanning attentiveness (Aston-Jones et al. 1999). An additional point is that an optimal amount of PFC activation, perhaps governed by 5-HT/NE balance, may help produce optimal mental health and cognition. Ramos and Arnsten (2007) suggest that moderate levels of NE released under normal conditions strengthen PFC function via action at postsynaptic alpha2A receptors with high affinity for NE, whereas high levels of NE release during stress impair PFC function via alpha1 and possibly beta1 receptors with lower affinity for NE. Arnsten (2009) proposes that optimal amounts of NE are released in PFC when we are alert or interested in something.

PFC is not a functionally or structurally homogeneous entity (Liston et al. 2006), so perhaps a given transmitter such as 5-HT does not uniformly activate the entire structure, including potential differences in hemispheric lateralization. For example, NE may play a particular role in task-related behaviors mediated by the orbitofrontal cortex (Aston-Jones and Cohen 2005). However, perhaps one can say that 5-HT, for example, principally activates PFC. Additionally, perhaps 5-HT and NE, acting as neuromodulators of the PFC, can transform the functional properties of this brain region, without being limited in their roles to just activation and deactivation. If the activation/deactivation hypothesis is indeed correct, it would be informative to further investigate the neural mechanisms through which these effects are achieved (Ramos et al. 2006; Wang et al. 2007). For example, one simple possibility is that 5-HT releasing neurons synapse directly onto glutamatergic cell types in particular circuits within the PFC, whereas NE releasing cells activate GABAergic cell types in the same or other circuits. However, many other circuit-based possibilities could exist that are more complex and less direct than this simple scenario.

As an alternative to the activation/deactivation hypothesis, if *both* 5-HT and NE activate the PFC, or both activate a subset of its functional properties (Chamberlain et al. 2006; Robbins and Roberts 2007; Aston-Jones and Cohen 2005) and/or subregions, endogenous variability in these two transmitter systems may still result in large variability in functional PFC activation across individuals of a given species.

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