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Deficits in Attentional Control: Cholinergic Mechanisms and Circuitry-Based Treatment Approaches

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Abstract

The cognitive control of attention involves maintaining task rules in working memory (or "online"), monitoring reward and error rates, filtering distractors, and suppressing prepotent and competitive responses. Weak attentional control increases distractibility and causes attentional lapses, impulsivity and attentional fatigue. Levels of tonic cholinergic activity (changes over tens of seconds or minutes) modulate cortical circuitry as a function of the demands on cognitive control. Increased cholinergic modulation enhances the representation of cues, by augmenting cue-evoked activity in thalamic glutamatergic afferents, thereby increasing the rate of detection. Such cholinergic modulation is mediated primarily via α4β2* nicotinic acetylcholine receptors. Animal experiments and clinical trials in adult patients with ADHD indicate that attentional symptoms and disorders may benefit from drugs that stimulate this receptor. Tonic cholinergic modulation of cue-evoked glutamatergic transients in prefrontal regions is an essential component of the brain's executive circuitry. This circuitry model guides the development of treatments of deficits in attentional control.

Keywords

Attention; Top-down Control; Cognitive Impulsivity; Acetylcholine; Glutamate; Nicotine; Dopamine

Control of attention in health and disease

Picture yourself working as an air traffic controller. Your task is to follow several aircraft represented as blinks on your screen, ensuring separation, altitude, speed, direction, and so forth. At the same time you are constantly checking for new planes entering your sector, and perhaps you are also receiving information about the changing status in adjacent sectors and watch an incoming storm front. These tasks require an enormous capacity for sustaining and shifting attention, over relatively long periods of time, and the management of attentional resources across competing sub-tasks.

Which are the mechanisms that suppress the urge to disengage from this task at regular intervals, to dream about your upcoming vacation, or simply to take a break from watching an array of monitors and instead look out of the window? Which are the mechanisms that

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allow you to filter intruding thoughts about pleasurable activities or the troubles in your family? In short, what controls sustaining attention to the task and minimizes distractibility?

Attentional control mechanisms (Figure 1) are severely impaired in patients with neuropsychiatric and neurodegenerative disorders, including schizophrenia and ADHD. Beginning with Kreapelin's (1912) rather modern, dynamic conceptualization of the long-term consequences of the increased distractibility of schizophrenic patients for their conception of the world, and followed by the description and classification of patients' self-reports by McGhie and Chapman (1961) ("…I jump from one thing to another…it's difficult to concentrate on any one sound…"), contemporary research has continued to classify the limited attentional resources and poor attentional control as hallmarks of, and perhaps essential contributors to, the cognitive impairments of these patients (e.g., Elvevag, Weinberger, Suter, & Goldberg, 2000; Lesh, Niendam, Minzenberg, & Carter, 2011; Luck, Ford, Sarter, & Lustig, 2011; Luck & Gold, 2008; Nuechterlein, Luck, Lustig, & Sarter, 2009; Silver & Feldman, 2005). Moreover, theories have continued to postulate that the emergence of positive symptoms is causally related to attentional control deficits. Such deficits allow irrelevant items to become attentionally bound and therefore signifiant components of the perception of a scene (e.g., Collerton, Perry, & McKeith, 2005). Therefore, such items gain control of behavioral and cognitive processes and further impair the efficacy if attentional control. The more these interacting processes escalate "…the less coherent and uniform is the conception of the external world" (Kraepelin, 1912; p. 22).

Deficits in "top-down" or "executive" control have also been conceptualized as an overarching cause of the attentional impairments and the impulsivity of patients with ADHD (e.g., Corkum & Siegel, 1993; Gorenstein, Mammato, & Sandy, 1989). Distractibility, lapses and fluctuations of attentional performance may not represent secondary consequences of primary impairments in response inhibition and impulsivity (e.g., Oosterlaan & Sergeant, 1998). Rather, inattention and impulsivity in ADHD are hypothesized to reflect a deficient executive, prefrontal control system (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006; see Fig. 1).

Motivational deficits are also present in patients with ADHD or schizophrenia. The relationships between motivational and attentional symptoms are poorly understood (e.g., Cubillo, Halari, Smith, Taylor, & Rubia, 2011; Douglas & Parry, 1994; Gorissen, Sanz, & Schmand, 2005). Abnormalities in the perception and processing of rewards, including a preference for immediate reward (Luman, Oosterlaan, & Sergeant, 2005; Sonuga-Barke, 2002; Volkow, et al., 2010) may contribute to, but also result from, poor cognitive control mechanisms (Haenlein & Caul, 1987).

Consequences of poor attentional control: distractibility and lapses, impulsivity, low motivation to perform and attentional fatigue

"Top-down", "executive" or "cognitive" control of attention concerns a set of broadly defined mental mechanisms which act collectively to sustain attentional performance, particularly in response to challenges such as distractors. These mechanisms include; (1) maintaining task-rules, including switching rules, and behavioral goals in working memory (or "online"); (2) performance monitoring, specifically error monitoring; (3) weighing reward and reward loss against levels of motivation; (4) recruiting mechanisms, such as enhanced cue processing and distractor filtering, to combat performance decline; and (5) suppression of prepotent responses and competitive behaviors (Figure 1; e.g., Baluch & Itti, 2010; E. K. Miller & Cohen, 2001; Pessoa, Rossi, Japee, Desimone, & Ungerleider, 2009; Rossi, Pessoa, Desimone, & Ungerleider, 2009; M. Sarter, Gehring, & Kozak, 2006; Woods

& Sarter, 2010). As will be described next, a weakening of these mechanisms are hypothesized to cause a wide spectrum of impairments in attention.

Distractibility and lapses

Distractibility is a cognitive construct that describes the increased probability for erroneous detection of (irrelevant) stimuli. Posner and colleagues (Posner, Snyder, & Davidson, 1980) defined detection as "…*the entry of information concerning the presence of a signal into a system that allows the subject to report the existence of the signal by an arbitrary response indicated by the experiment*". Erroneous detections can be triggered by salient stimuli or stimuli with unique features (often called "feature singletons"). Furthermore, weak top-down control of attention to the search field, object group or scene is a fundamental prerequisite for committing false detections (e.g., Theeuwes & Godijn, 2002).

Neurophysiological studies demonstrated that erroneous detection begins with the representation of a non-target cue in primary sensory regions (e.g., Roelfsema & Spekreijse, 2001). As will be discussed further below, such representation may not be sufficient for (false) detection. Likewise, weak signals may evoke an orienting response but they are not necessarily detected. The efficacy with which cues are amplified and distractors are filtered indicate the strength of attentional control processes. Cue amplification and distractor filtering are less effective if the demands on cognitive control are already high and if there is competition among stimuli (e.g., Lavie, 2005). fMRI studies have generated evidence in support of both cue amplification and distractor filtering as main mechanisms activated to combat distractibility (Polk, Drake, Jonides, Smith, & Smith, 2008). In the presence of explicitly defined distractors, as is the case with most laboratory tasks, evidence seems to favor neuronal mechanisms acting to enhance the processing of target cues (Nieuwenhuis & Yeung, 2005; Weissman, Warner, & Woldorff, 2004).

There are conceptual overlaps between the nature of, and the attentional mechanisms underlying, attentional lapses and increases in distractibility. Lapses may involve erroneous detection but more typically refer to *failures* to detect and errors of action, such as erroneous repeats of responses, unintended responses, and omissions that reflect detection failures (as opposed to loss of motivation; e.g., Reason, 1984). The primary source for such lapses are failures to keep the task-rules "online", to stay-on-task (see Manly, Robertson, Galloway, & Hawkins, 1999), to resist attentional distraction (e.g., Leber, 2010), and to suppress competitive behaviors, the latter leading to unintended responses. Imaging (Eichele, et al., 2008; Weissman, Roberts, Visscher, & Woldorff, 2006) and neurophysiological (O'Connell, et al., 2009) studies in humans, as well as our real-time recordings of prefrontal cholinergic activity in rats (Parikh, Kozak, Martinez, & Sarter, 2007) demonstrated that such lapses can be predicted as early as 20–30 sec prior to their occurrence, by measuring neuronal markers indicating insufficient suppression of task-irrelevant neuronal activity and decreases in task-relevant brain activity.

Impulsivity

In the specific context of attentional task performance, impulsivity first concerns the frequent and compulsive disengagement from task performance (often termed, motor impulsivity). This form of impulsivity involves readily activated sets of complex yet fixed action patterns, such as grooming, exploration, locomotion, climbing, and fidgeting, all of which interfere with task performance. Deficits in the processing of time (Castellanos, et al., 2006) may foster the frequent execution of these motor programs.

Second, impulsivity concerns the failure to cancel or inhibit a specific behavioral response and, depending on task demands, to inhibit one response to execute a different, correct

response. This more specific form of impulsivity often involves attentional reorientation and repositioning that is not controlled by task stimuli (impulsive action; Winstanley, Eagle, & Robbins, 2006; Winstanley, Olausson, Taylor, & Jentsch, 2010). A range of cognitive mechanisms may increase the propensity for such impulsive responses, including a weak "online" representation of the task rules. Both forms of impulsivity can be conceptualized as consequences of cognitive control deficits (e.g., Nigg, 2003). Weak cognitive control diminishes the capacity to suppress prepotent responding and competitive behaviors, and to sustain attention to the source of target cues and maintaining task-rules in working memory.

It is important to note that although symptoms of impulsivity and hyperactivity often are lumped together to describe the hyperkinetic component of ADHD, the performance of patients in structured tasks is not necessarily contaminated by impulsive and hyperkinetic responsivity. Rather, response latencies and frequencies of ADHD patients may remain below those of control subjects (Carte, Nigg, & Hinshaw, 1996; Casey, et al., 1997) and thus more generally reflect poor cognitive control (see also Oosterlaan & Sergeant, 1998; Suskauer, et al., 2008). Similar to the demonstration of hyperactivity in animal models, requiring the absence of structured and behavior-constraining demands on performance (see, e.g., the absence of hyperkinetic symptoms in rats treated with an escalating dosing regimen of amphetamine and performing an attention task; Kozak, et al., 2007; Martinez, Parikh, & Sarter, 2005), it appears that demonstration of the hyperkinetic symptoms in patients is fostered by the absence of cognitive demands and controlled task performance.

Low motivation for attention/attentional fatigue

The bidirectional, intricate relationships between motivational processes and levels of attentional performance (e.g., Engelmann & Pessoa, 2007; Mischel & Ebbesen, 1970; Savine & Braver, 2010; Small, et al., 2005; St. Peters, Demeter, Lustig, Bruno, & Sarter, 2011) challenge the determination of individual mechanisms responsible for controlling performance changes (see also Frith, 2001). Indeed, attentional control and reward mechanisms have been suspected to remain conceptually, experimentally, and neuronally inseparable (Gottlieb & Balan, 2010; Maunsell, 2004). For example, a decrease in the value of a reward weakens the impact of unrewarded misses or false alarms and thus may evoke an only limited recruitment of processes for recovering response accuracy, yielding further performance decline. Importantly, however, reward perception is not merely a function of the subject's degree of motivational saturation but is also influenced top-down. For example, prolonged sustained attention is associated with increasing demands on top-down control to suppress switching to alternative or competitive behaviors; such increases in "task difficulty" result in a discounting of the value of trial-based reward ("effort discounting"; Botvinick, Huffstetler, & McGuire, 2009; Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009). Thus, poor or exhausted attentional control mechanisms and associated effort discounting interact to further impair attentional performance, eventually generating performance levels that correspond with those expected from subjects with generally low levels of motivation (e.g., Sykes, Douglas, & Morgenstern, 1973). Omitting a majority of trials or even disengaging from task may rarely indicate motivational saturation, specifically in experiments with humans who typically perform for negligible rewards. Rather, low motivation to perform in attention tasks is a consequence of weakened attentional control and thus may be better termed "attentional fatigue" (e.g., Lim, et al., 2010). Challenges that tax top-down control mechanisms, such as the presentation of distractors, are particularly effective in evoking periods of attentional fatigue (e.g., Demeter, Sarter, & Lustig, 2008).

Tonic and phasic cholinergic mediation of attention

Below we will review the evidence indicating that the tonic component of cortical cholinergic neurotransmission modulates cortical circuitry and the efficacy of attention as a

function of the demands on top-down control. The circuitry model describing the regulation and function of the cortical, specifically prefrontal cholinergic input system postulates that a branch of the cholinergic system is tonically active (changes over tens of seconds to several minutes) and modulates primarily, but likely not exclusively, the glutamatergic terminals of afferent arising from the mediodorsal thalamic nucleus (Hasselmo & Sarter, 2011). As will be further detailed below, this cholinergic activity modulates the prefrontal representation of cue salience and thereby, necessarily but not sufficiently, cue detection and attentional performance.

Cholinergic activity modulates glutamate released from thalamic inputs primarily by stimulating α4β2* nicotinic acetylcholine receptors (nAChRs) that are expressed at the terminals of these thalamic afferents (Howe, et al., 2010; Lambe, Picciotto, & Aghajanian, 2003; Parikh, Ji, Decker, & Sarter, 2010; Parikh, Man, Decker, & Sarter, 2008; M. Sarter, Parikh, & Howe, 2009). Separate from this tonic component of the cortical cholinergic input system, local cortical circuitry, including glutamate release events from thalamic afferents, generates a brief cholinergic release event ("transient"; scale of seconds; Figure 2). In attentional task-performing animals, this cholinergic transient is necessary for a cue to be detected or, in other words, for the animal to score a hit (Parikh, et al., 2007; Parikh & Sarter, 2008). The probability for such cholinergic transients to occur is modulated indirectly by the tonic component of cholinergic neurotransmission and its effects on cue-evoked glutamate release. Additional neuronal mechanisms, including GABAergic interneurons, also influence the generation of cholinergic transients (e.g., Berry, et al., 2011).

Measuring tonic cholinergic activity versus cholinergic transients

A methodological corollary of this scheme concerns the methods used to measure and to differentiate between tonic cholinergic neurotransmission and cholinergic transients (microdialysis versus enzyme-coated microelectrodes/amperometry). Of particular importance in this context is evidence indicating that measures of tonic levels of cholinergic activity, measured by using microdialysis and collection periods over several minutes, do not merely represent integrated transients as measured by amperometry. First, manipulations that reduce the probability of transients in animals performing a sustained attention task (SAT; described below), such as distractor presentation, elevate tonic levels of cholinergic neurotransmission (below). Second, drugs that enhance cue detection and thus produce more cholinergic transients at the same time reduce levels of tonic cholinergic activity (Paolone, Howe, Gopalakrishnan, Decker, & Sarter, 2010). Both examples indicate opposite effects on tonic cholinergic activity and the number of cholinergic transients, rejecting the hypothesis that dialysates collected over minutes merely indicate the integration of second-based transients. The reasons why microdialysis appears to be optimized for detecting tonic levels of acetylcholine (ACh) that are not contaminated by transients are not fully understood but may be due in part to the formation of a glial-derived diffusion barrier that encapsulated the probe (Jaquins-Gerstl & Michael, 2009).

Attentional performance-associated tonic cholinergic activity and the nature of cholinergic top-down control

Augmented increases in tonic cholinergic activity

The evidence reviewed in this section has largely been obtained from experiments in which ACh release was measured while animals performed a sustained attention task (SAT), including a version during which a distractor (dSAT) was presented during several blocks of trials. Briefly, this task consists of a random sequence of unpredictable signal events or blanks following which two (species-specific) manipulanda become available for a restricted

time. The subject reports the prior presence or absence of a signal by operating one or the other manipulanda (retractable levers in rats, keys in humans, retractable nose ports ("MICARPS"; St Peters, Cherian, Bradshaw, & Sarter, 2011) in mice). Rewarded responses are hits and correct rejections, respectively, while misses and false alarms are not rewarded and trigger a variable intertrial interval. Task versions have been developed and validated for testing mice, rats and humans (for details see Demeter, Hernandez-Garcia, Sarter, & Lustig, 2011; Demeter, et al., 2008; McGaughy & Sarter, 1995; Nuechterlein, et al., 2009; St Peters, et al., 2011).

Early studies on the effects of selective removal of the cortical cholinergic input system demonstrated that such lesions resulted in the robust, permanent and selective impairments in the detection of signals, while sparing response accuracy in non-signal trials (McGaughy, Kaiser, & Sarter, 1996; McGaughy & Sarter, 1998). Although this evidence established the necessity of the cortical cholinergic input system for cue detection, such lesions disrupt all modes of cholinergic neurotransmission and thus effects cannot be attributed solely to the absence of tonic cholinergic activity.

SAT performance has been frequently demonstrated to increase levels of ACh release, in prefrontal, anterior and posterior parietal regions. Performance of various procedures controlling for effects of lever pressing rate, reward rate, and sensory effects of stimuli consistently indicated that such increases in release are not reproduced in the absence of demands on sustained attention (Arnold, Burk, Hodgson, Sarter, & Bruno, 2002; Himmelheber, Sarter, & Bruno, 1997, 2000, 2001; Kozak, Bruno, & Sarter, 2006; Kozak, et al., 2007). However, while SAT performance reliably increases ACh release by 100–140% (over basal levels), release levels were not found to correlate with measures of performance. In the past, the considerable variability of measures of ACh release in performing animals was speculated to prevent the demonstration of such relationships. This view was rejected by more recent studies that attributed a different cognitive function to levels of ACh release associated with attentional performance.

In 2006, Kozak and colleagues observed that in animals performing the SAT, blockade of NMDA receptors in the basal forebrain resulted in impairments in detection performance that dose-dependently stabilized and recovered towards the end of the session (and about 30 min after infusions). During this late period, performance-associated increases in ACh release were found to be augmented over regular SAT performance-associated increases in ACh release, reaching over 200% over baseline in the last collection interval (Kozak, et al., 2006). This finding formed the basis for the hypothesis that the degree of cognitive control of attention taxed by task conditions, not levels of performance, are correlated with levels of ACh release (M. Sarter, et al., 2006). In other words, the greater the demands for cognitive control mechanisms the greater the tonic cholinergic modulation of cortical circuitry.

This hypothesis was tested in a recent study in which SAT performing rats were exposed to a distractor in the 2nd and 3rd out of a total of 5 blocks of 8-min trials. Performance during the distractor (houselights falling on-off at 0.5 Hz) period was impaired and, depending on the individual measures of performance, plateaued or began to recover during the second distractor period. ACh release was highest during the two distractor periods, peaking at about 180% over baseline (and compared with 90–100% over baseline and in the absence of the distractor). Most importantly, release levels were significantly correlated with performance, with less severe distractor effects on performance associated with higher release levels (St. Peters, et al., 2011). Using a measure that collapses signal and non-signal trial performance into one score (SAT score, ranging from zero {random response selection} to 1 {perfect performance}), better dSAT performance by one unit of the SAT score (0.1)

was associated with an additional 38% increase in ACh release (see Figure 1 in St. Peters, et al., 2011).

To stabilize and recover performance in the presence of a distractor, subjects are required to enhance the processing cues, filter distractors, suppress the perhaps impulsive tendency to disengage from task, and to maintain motivation to perform (note that omission remained low in the experiment described above). Presumably, these mechanisms are activated by the onset of the distractor and the loss of reward early into the first distractor period (as the animals commit significantly more misses and false alarms). ***Augmented levels of tonic cholinergic activity are hypothesized to represent a main mechanism via which attentional control mechanisms are recruited and their efficacy is increased.***

Relationship between increases in cholinergic activity and fMRI-based activity measures

Using arterial spin labeling (ASL) fMRI, dSAT performance of healthy humans was correlated with increases in activity in the (right) middle frontal gyrus (Demeter, et al., 2011). This correlation was orthogonal to that observed between the severity of the distractor effect and cholinergic activity (St. Peters, et al., 2011). Specifically, in humans, greater activity was correlated with more severe effects of the distractor on performance. In animals, higher levels of cholinergic neurotransmission predicted better residual performance (above). We hypothesize, therefore, that higher levels of cholinergic activity optimizes prefrontal circuitry, by reducing neuronal noise patterns and network fluctuations (e.g., Cohen & Maunsell, 2009; Leber, 2010), and thereby reduces demands on metabolic supply and consumption of this region.

Mesolimbic control of augmented tonic cholinergic activity

The “top in top-down control” (B. T. Miller & D’Esposito, 2005) has been attributed to the prefrontal regions (Pessoa, et al., 2009; Rossi, et al., 2009). However, exactly what information recruits top-down control mechanisms, and via what neuronal circuitries and mechanisms, has remained largely unclear. Research on such mechanisms has focused on demonstrating altered neuronal processing in extra-prefrontal cortical regions as a result of prefrontal manipulations, or on studying the time course of the transfer of information from prefrontal to extra-prefrontal regions. Medial prefrontal regions calculate prediction errors and are thought to initiate corrective action by recruiting dopaminergic mesolimbic regions to modify performance (e.g., Modirrousta & Fellows, 2008; Rutledge, Dean, Caplin, & Glimcher, 2010; Schultz, 2006; S. F. Taylor, et al., 2006). Thus, the loss of rewards early in the distractor block, and perhaps also the perception of distractors *per se*, may be sufficient to activate prefrontal efferent systems and attention-supporting neuronal mechanisms to maintain and recover performance under challenging conditions.

The prefrontal cortex provides direct glutamatergic feedback to the basal forebrain and, indirectly, also via projections to mesolimbic regions, including the nucleus accumbens (NAC), ventral tegmentum and the amygdala. All these mesolimbic regions project to the cholinergic basal forebrain (see Figure 1 in M Sarter & Lustig, 2009; Zaborszky, 2002; Zaborszky, Buhl, Pobalashingham, Bjaalie, & Nadasdy, 2005; Zaborszky & Cullinan, 1992, 1996; Zaborszky, Cullinan, & Luine, 1993; Zaborszky, Gaykema, Swanson, & Cullinan, 1997; Zaborszky, Heimer, Eckenstein, & Leranth, 1986; Zaborszky, Leranth, & Heimer, 1984; Zaborszky, Pang, Somogyi, Nadasdy, & Kallo, 1999). Given the evidence indicating that the NAC processes information about instrumental effort (e.g., Farrar, et al., 2008; e.g., Font, et al., 2008; e.g., Mingote, et al., 2008), we investigated the possibility that NAC-basal forebrain interactions contribute to tonic cholinergic activity, specifically in situations taxing attentional control.

NAC neuronal activity is necessary to demonstrate performance-associated increases in cortical cholinergic neurotransmission (Neigh, Arnold, Rabenstein, Sarter, & Bruno, 2004). Furthermore, stimulation of ionotropic glutamate receptors in the NAC shell selectively stimulates ACh release in prefrontal regions (Zmarowski, Sarter, & Bruno, 2005, 2007). Thus we hypothesized that such stimulation benefits the attentional performance specifically in the presence of a distractor.

SAT performing animals were equipped with guide cannula to allow the remote infusion of NMDA into the NAC *while* performing the SAT. Following a first block of undisturbed performance, NMDA was infused into the NAC, shell or core, and either SAT continued or the distractor was presented following another 8-min block of regular performance. NAC infusions did not affect SAT performance. Furthermore, performance in the presence of the distractor did not benefit from infusions into the core of the NAC. In contrast, infusions into the NAC shell improved the performance in the presence of a distractor. This improvement reached a level that was statically similar to the performance seen in the absence of the distractor (and of infusions). Furthermore, we also demonstrated that the beneficial effects of NMDA NAC shell infusions required the presence of cholinergic projections to the PFC (St. Peters, et al., 2011).

These findings indicate that the NAC, presumably based on its afferents from prefrontal and other mesolimbic regions and its GABAergic projections to cholinergic cells of the basal forebrain (above), represents a major component of the efferent projection systems of the prefrontal cortex that mediates top-down effects. NAC-basal forebrain interactions are activated in situations requiring the enhanced cognitive control of attentional performance. The effects of NAC NMDA infusions suggest that activation of NAC circuitry is sufficient to attenuate the detrimental performance effects of distractors.

The effects of NAC stimulation on dSAT performance cannot be interpreted in simple terms of enhanced motivation. First, such stimulation did not improve SAT performance (no distractor). Second, the distractor did not robustly increase the number of errors of omission and NAC NMDA receptor stimulation did not affect omission rates. Thus, NMDA infusions did not simply increase the animals' instrumental effort. An important third and related argument concerns the finding the NAC NMDA receptor stimulation selectively benefited the animals' detection rate. This finding is consistent with the hypothesis that augmented cholinergic activity benefits dSAT performance specifically by enhancing the neuronal mechanisms that mediate the likelihood for signal detection. These mechanisms are described next.

Tonic cholinergic enhancement of thalamic glutamatergic representation of signals

As already mentioned, neuropharmacological experiments involving mice lacking nAChR subtypes demonstrated that cholinergic activity modulates the activity of mediodorsal thalamic (MD) glutamatergic afferents via α4β2* nAChRs expressed at these neurons' terminals (references above; see also Guillem, et al., 2011; Lambe, et al., 2003).

Thalamic glutamatergic projections are thought to "import" a pre-attentional representation of the cue into the prefrontal detection circuit. For a signal to be detected it first needs to undergo sensory analysis and coding, and be identified as a component of a group of stimuli that are potential targets for attention ("coarse categories"; Logan, 1992; Treisman, Vieira, & Hayes, 1992). The neuronal circuitry that generates such preattentional representation of stimuli includes the projections from sensory regions to the thalamic reticular nucleus and reticular projections to the MD (e.g., Guillery, Feig, & Lozsadi, 1998; Pinault, 2004).

Consistent with this hypothesis, amperometric recordings of signal-evoked glutamatergic release events in the middle layers of the PFC of SAT performing animals indicate that all signals, irrespective of subsequent detection, evoke glutamatergic transients. Furthermore, the amplitude of such transients codes signal salience, but only in well-performing animals. During poor performance periods glutamatergic signal amplitudes are attenuated and salience-coding is lost. This findings indicate that these cue-evoked glutamate release events are modulated (Howe & Sarter, 2010).

Stimulation of α4β2* nAChRs is hypothesized to augment signal-evoked glutamatergic transients and was demonstrated, as predicted by this hypothesis, to enhance the detection of cues (Howe, et al., 2010). Larger glutamatergic transients are more likely to evoke a cholinergic transient and thus mediate detection (Parikh, et al., 2008). Note again that, in contrast to glutamatergic transients, cholinergic transients are not evoked by signals that are missed, and unlike glutamatergic transients, they are not modulated in graded manner (Figure 2).

Tonic cholinergic control of attention

Collectively, and in somewhat simplified terms, this evidence suggests the following general scenario. During attentional performance, presentation of a distractor causes misses and false alarms and thus reward loss. This loss is computed in prefrontal regions and triggers recruitment of prefrontal efferents to mesolimbic regions which converge primary on NAC outputs to the basal forebrain, increasing tonic cholinergic activity of corticopetal projections. As a result of such upregulation of tonic cholinergic activity, the preattentional representation of signals is amplified and thus these signals are more likely to be detected. Clearly, this simplified description obscures numerous key issues that remain to be addressed, including the possibility that top-down effects on cholinergic activity manifest cortex-wide and may also involve cortico-cortical mechanisms (Nelson, Sarter, & Bruno, 2005).

Animals exhibiting poor attentional control

The neuronal origin of poor cognitive control of attention remains not well understood. We are in need of animal models that are characterized by low tonic cholinergic activity and poor cognitive control, to study the development of attentional symptoms and their escalating contributions to other psychiatric symptom clusters. Preliminary evidence from our studies suggests that rats with these characteristics are present in outbred populations and can readily be identified by assessing their propensity to approach a stimulus associated with reward delivery. Animals classified as “sign-trackers” (Flagel, Akil, & Robinson, 2009; Flagel, Watson, Akil, & Robinson, 2008; Flagel, Watson, Robinson, & Akil, 2007; Lovic, Saunders, Yager, & Robinson, 2011; Saunders & Robinson, 2010, 2011) exhibit a high frequency of periods of extremely poor SAT performance, approaching random response selection. Impulsive action, that is, the inability to inhibit responding to the incorrect lever should animals be positioned in front of that lever as it is extended, represents a substantial source for these poor periods of performance (Paolone, Angelakos, Meyer, Robinson, & Sarter, 2011). Importantly, these animals are able to periodically perform as well as their consistently well-performing counterparts (“goal-trackers”); therefore, their impairments cannot simply be accounted for by assuming more fundamental deficits in sensory coding or bottom-up attentional processes.

Circuitry-derived cholinergic treatment of poor attentional control

Our current understanding of the role of tonic cholinergic activity in the control of attention and the underlying neuronal circuitry suggests a rather straightforward therapeutic approach

to benefit poor cognitive control of attention. Stimulation of α4β2* nAChRs is hypothesized to specifically improve the detection rate of subjects performing attention tasks (Howe, et al., 2010; McGaughy, Decker, & Sarter, 1999; Mohler, et al., 2010; K. Taylor, Decker, Sarter, & Parikh, 2011). We have also began to explain why acetylcholinesterase inhibitors and nicotine are not as effective as α4β2* nAChR agonists. These reasons include the excessive extra-synaptic availability of ACh and the resulting presynaptic inhibition resulting from high ACh levels that is caused by esterase inhibitors, and the stimulation of the α7 nAChR resulting from both such inhibitors and the administration of nicotine (for details see Howe, et al., 2010; M.S arter, Lustig, & Taylor, 2011).

The predictive validity of this preclinical evidence is indicated by the results from clinical trials showing that α4β2* nAChR agonists improve the attention of adult (Apostol, et al., 2011; Wilens, et al., 1999; Wilens, Verlinden, Adler, Wozniak, & West, 2006) but not pediatric (Wilens, et al., 2011) patients with ADHD. These effects of α4β2* nAChR agonists have been considered promising given the limited cognitive benefits of psychostimulants in adult ADHD patients (reviewed in Wilens & Decker, 2007). In the present context, the failure of a α4β2* nAChR agonist to robustly improve attention in pediatric ADHD patients may be speculated to be consistent with our hypothesis that such compounds specifically enhance the cognitive control of attention. Given that cognitive control mechanisms continue to mature into the third decade of life (e.g., Andrews-Hanna, et al., 2011), it seems likely that different cognitive mechanisms underlie the attentional impairments and impulsivity of pediatric versus adult patients with ADHD. As the field focused on describing overlapping symptom and associated brain activity and describing adult ADHD as continual disorder (e.g., Cubillo, et al., 2011), little appears to be known about the cognitive mechanisms which potentially differentiate between pediatric and adult ADHD. If it the attentional symptoms of adult ADHD were a more direct result of weak cognitive control of attention than is the case in pediatric patients, α4β2* nAChR agonists would be expected to benefit primarily the adult version of the disorder.

The preclinical evidence also suggests that it is worthwhile to assess α4β2* nAChR agonists as adjunct treatment for improving the cognitive symptoms of patients with schizophrenia (M. Sarter, et al., 2011). However, there is presently little knowledge about the putative interactions between the effects of α4β2* nAChR agonists, antipsychotic drugs and high smoking rates; these issues require study to predict the usefulness of such adjunct treatment trials (K. Taylor, et al., 2011).

CONCLUSIONS

This review postulates the following main hypotheses: (1) Distractibility, impulsivity, attentional lapses, low motivation to perform attention tasks and attentional fatigue all are consequences of poor cognitive control of attention. (2) The tonic component of the cortical cholinergic projection systems modulates cue detection processes as a function of the degree of top-down control. (3) Prefrontal-mesolimbic circuitry, specifically the NAC projections to the cholinergic basal forebrain, contribute to the activation of the cholinergic system in situations characterized by demands on cognitive control of attention. (4) Stimulation of α4β2* nAChRs mimics and presumably amplifies the tonic cholinergic modulation of cortical circuitry and thus benefits attentional control mechanisms.

While our understanding of the regulation and function of cholinergic activity has evolved and departed from traditional descriptions of this neuronal system as a unitary, reticular, arousal-mediating group of neurons, our knowledge of the temporal dynamics of the multiple modes of cholinergic activity remains rudimentary. Furthermore, our understanding of the neuronal causes of poor attentional control, specifically in disorders, is largely

undeveloped. Circuitry models such as shown in Figure 2 will evolve rapidly and undoubtedly become hugely more complex. Such models provide a framework for studying the neuronal mechanisms contributing to poor attentional control, they explain the limitations of traditional cholinomimetic treatment strategies (see also M. Sarter, et al., 2011) and they suggest treatments that have already been demonstrated to be effective inpatients with poor attentional control (Apostol, et al., 2011).

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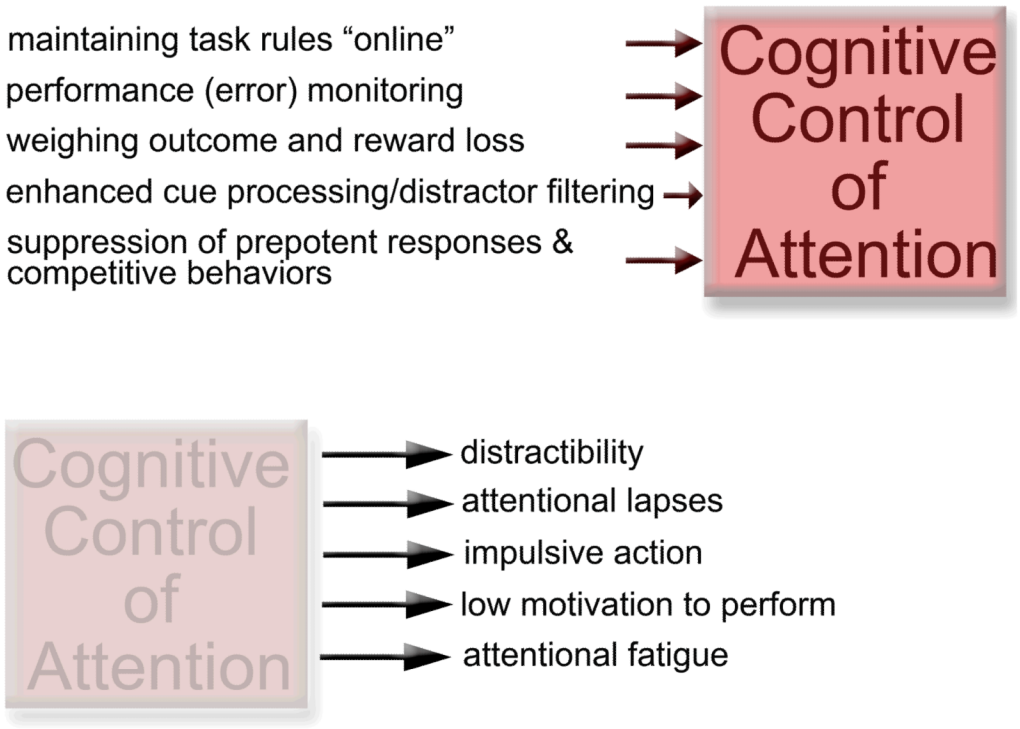

Figure 1.
Synopsis of the mental operations that constitute the construct “cognitive control of attention” (top) and of the consequences of weakened top-down control (symbolized by the transparent box) for attentional performance (bottom).

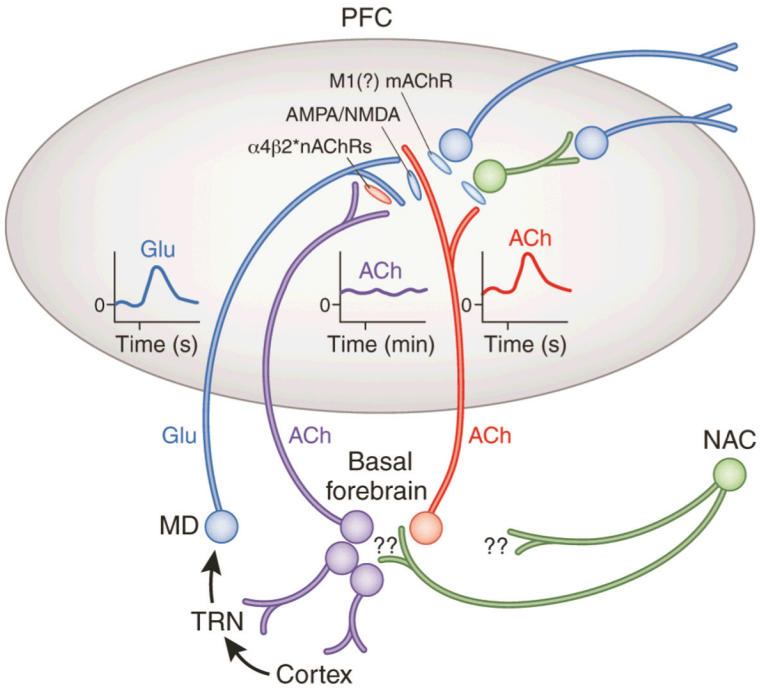

Figure 2.

Circuitry model describing the main components of the prefrontal cortex (PFC) circuitry mediating signal detection and processing mode shifts. The model combines evidence with parsimonious assumptions required to explain electrochemical and attentional performance data (see main text for details). The glutamatergic (GLU) inputs to the PFC, originating from the mediodorsal thalamic nucleus (MD) "import" a preattentionally processed representation of the signal into the PFC (see text for definition). MD neurons are part of a network that includes the thalamic reticular nucleus (TRN) and its topographic afferents from sensory cortical regions. The cue-evoked glutamatergic transient (see insert) generates a cholinergic transient (see insert), via stimulation of ionotropic presynaptic glutamate receptors (Parikh, et al., 2010; Parikh, et al., 2008). This cholinergic transient mediates the actual detection process or, depending on the task, a processing mode shift that fosters detection (see main text). Prefrontal output neuron activity is stimulated by ACh primarily via muscarinic (m)AChRs, thereby organizing the behavioral responses that indicate successful detection.

The terminals of the MD inputs to the PFC are equipped with α4β2* nAChRs. Cholinergic stimulation of these receptors is thought to vary over minutes, refecting a tonic component of cholinergic neurotransmission (see elevated release illustrated by the insert). nAChR agonists enhance detection performance primarily by positively modulating GLU release from these terminals, thereby augmenting the amplitudes of the cholinergic transients (Howe, et al., 2010; Parikh, et al., 2010). This model therefore proposes two separate roles for cholinergic inputs, mediated via separate populations of cholinergic neurons. A rather tonically active cholinergic input modulates glutamate release from MD neurons which, in turn, target the terminals of a separate group of cholinergic neurons, generating the transients that enhance attentional orienting and cue detection. Reproduced, with permission of Nature Publishing Group, from Hasselmo and Sarter (2011; p. 58).