Review

The cognitive neuroscience of sustained attention: where top-down meets bottom-up

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Abstract

The psychological construct 'sustained attention' describes a fundamental component of attention characterized by the subject's readiness to detect rarely and unpredictably occurring signals over prolonged periods of time. Human imaging studies have demonstrated that activation of frontal and parietal cortical areas, mostly in the right hemisphere, are associated with sustained attention performance. Animal neuroscientific research has focused on cortical afferent systems, particularly on the cholinergic inputs originating in the basal forebrain, as crucial components of the neuronal network mediating sustained attentional performance. Sustained attention performance-associated activation of the basal forebrain corticopetal cholinergic system is conceptualized as a component of the 'top-down' processes initiated by activation of the 'anterior attention system' and designed to mediate knowledge-driven detection and selection of target stimuli. Activated cortical cholinergic inputs facilitate these processes, particularly under taxing attentional conditions, by enhancing cortical sensory and sensory-associational information processing, including the filtering of noise and distractors. Collectively, the findings from human and animal studies provide the basis for a relatively precise description of the neuronal circuits mediating sustained attention, and the dissociation between these circuits and those mediating the 'arousal' components of attention. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Beginning with Mackworth's experiments in the 1950s, the assessment of sustained attention (or vigilance) performance typically has utilized situations in which an observer is required to keep watch for inconspicuous signals over prolonged periods of time. The state of readiness to respond to rarely and unpredictably occurring signals is characterized by an overall ability to detect signals (termed 'vigilance level') and, importantly, a decrement in performance over time (termed 'vigilance decrement'). The psychological construct of 'vigilance', or 'sustained attention', has been greatly advanced in recent decades, allowing the development and validation of diverse tasks for the test of sustained attention in humans and animals and thereby fostering research on the neuronal circuits mediating sustained attention performance in humans and laboratory animals.

Sustained attention represents a basic attentional function that determines the efficacy of the 'higher' aspects of attention (selective attention, divided attention) and of cognitive capacity in general. Although impairments in the ability to detect and select relevant stimuli or associations are intuitively understood to impact modern living skills (e.g., driving a car), cognitive abilities (e.g., acquiring novel operating contingencies of teller machines, or detecting social cues important to communicate effectively), and possibly even consciousness [74], psychological research on sustained attention has largely focused on parametric, construct-specific issues and only rarely addressed the essential significance of sustained attention for higher cognitive functions like learning and memory [17]. In fact, the evidence in support of the fundamental importance of sustained attention for general cognitive abilities has largely been derived from studies in neuropsychiatric populations (see below). Thus, determining the brain networks mediating sustained attention not only represents a crucial step toward understanding the neuronal mechanisms underlying this critical cognitive function, but also toward the development of cognitive neuroscience-inspired theories of neuropsychiatric disorders characterized by impairments in fundamental attentional functions (see below).

Cognitive neuroscience research has consistently documented activation in right hemispheric prefrontal and parietal regions during sustained attention performance.

The recent overview by Cabeza and Nyberg [8] illustrates the sobering degree to which such imaging data remain isolated if they are not embedded in a theory describing the neuronal mediation of the cognitive performance of interest. As we have argued earlier [85], the development of such a theory requires converging evidence from studies manipulating the cognitive function of interest (i.e., sustained attention) and measuring brain correlates (typically human imaging studies) with results from experiments on the consequences of manipulations in the integrity, excitability, or integrative capacity of defined neuronal circuits on the cognitive function of interest (typically animal behavioral–neuroscientific studies). Such converging evidence ensures that research aimed at explaining complex high-level cognitive functions by successively lower neural levels of description benefits from neuroscientific research approaches, and that efforts to determine low-level neuronal mechanisms of cognitive functions benefit from cognitive construct-driven research in humans [25,63,76]. Furthermore, it is crucial that evidence in support of neuronal circuits acting top-down to modulate attentional information processing (e.g., Ref. [75]) will be integrated with evidence on the role of ascending cortical input systems to arrive at a comprehensive theory of sustained (or any other form of) attention. In other words, the title phrase 'where-top down meets bottom-up' reflects two interrelated issues, that is (1) the convergence of information generated by cognitive-neuroscience research in humans and by the more fundamental neurosciences that is required to attribute sustained attention to defined neuronal circuits [85], and (2) the convergence of the functions mediated via top-down cognitive processes and bottom-up sensory input processing that is crucial for sustained attentional performance. These convergences are the focus of this review, indicating that the different levels of analysis employed by cognitive neuroscience research on sustained attention have sufficiently developed, albeit largely separately, to permit now an integration of evidence and therefore the development of a theory about the neuronal mediation of sustained attention.

1.1. Top-down versus bottom-up

The terms 'top-down' and 'bottom-up' processes, and the special focus of this review, require further clarification. 'Top-down' or 'bottom-up' regulation of attentional

processes represent conceptual principles rather than referring to anatomical systems, such as ascending and descending projections. 'Top-down' processes describe knowledge-driven mechanisms designed to enhance the neuronal processing of relevant sensory input, to facilitate the discrimination between signal and 'noise' or distractors, and to bias the subject toward particular locations in which signals may appear [41]. For example, in sustained attention performance, the subject knows where to expect what type or modality of signal, how to respond in accordance with previously acquired response rules, and so forth. Furthermore, the subject develops expectations concerning the probability for signals and strategies for reporting signals versus false alarms (see below). All these variables influence performance, based on mechanisms that range from changes in sensory signal processing to the enhanced filtering of distractors and the modification of decisional criteria.

Such a 'top-down' biasing of attentional performance contrasts with 'bottom-up' perspectives that describe attentional functions as driven mainly by the characteristics of the target stimulus and its sensory context [97]. 'Bottom-up' perspectives attempt to explain a subject's ability to detect targets and target-triggered attentional processing largely by the sensory salience of the targets, and their ability to trigger attentional processing by recruiting 'higher' cortical areas in a bottom-up manner (e.g., from the processing of a visual target in the primary visual cortex to temporal regions for object identification and to parietal regions for location). Importantly, 'top-down' and 'bottom-up' processes represent overlapping organizational principles rather than dichotomous constructs, and in most situations, top-down and bottom-up processes interact to optimize attentional performance [22].

Activation of top-down processes are traditionally considered a component of the frontal cortical mediation of executive functions. Such processes were previously conceptualized in the context of attention by Posner and Petersen's [75] anterior and posterior attention systems that function to detect targets and bias the subjects' orientation to target sources, respectively. Data from human imaging and primate single unit recording studies have substantiated the notion of top-down processes by demonstrating sequential activation of frontal-parietal–sensory regions, including decreases in activity in task-irrelevant sensory regions, and the modulation of neuronal activity in sensory and sensory-associational areas reflecting the top-down functions described above [19,39,41,93]. This review focuses on the functions of the basal forebrain cholinergic projections to the cortex as a major component of the activation of top-down processes in the mediation of sustained attention. To avoid confusion, it should be reiterated that therefore, the *anatomically ascending* basal forebrain system is proposed to contribute to the *functionally top-down* processes in sustained attention.

As will be discussed below, the activation of cortical cholinergic inputs as a major component of the top-down processes in sustained attention performance acts to bias the processing of sensory inputs at all levels of cortical sensory information processing, thereby facilitating and maintaining sustained attention performance. Fig. 1 captures this hypothesis by illustrating the anterior attention system and its top-down regulation of posterior and sensory cortical information processing ([75]; see also legend for Fig. 1). The basal forebrain cholinergic corticopetal projection system is conceptualized as a major and necessary component of these top-down processes. In sustained attention, this projection system is activated, via direct connections from the prefrontal cortex to the basal forebrain. Increased activity in cortical cholinergic inputs, that terminate in all cortical regions and layers, facilitate all aspects of the top-down regulation of sustained attention performance, ranging from the enhanced sensory processing of targets to the filtering of distractors and the optimization of decisional strategies. Evidence in support of this hypothesis will be discussed in detail, following a description of the construct 'sustained attention'.

2. Sustained attention: components of a construct

2.1. 'Sustained attention' and 'arousal': conceptual overlaps and differences

As the terms 'vigilance/sustained attention' and 'arousal' have been used interchangeably, particularly in clinical contexts and in interpreting electroencephalographic (EEG) data, the specific meaning of vigilance/sustained attention needs to be defined and dissociated from the more global classification of brain states that include 'arousal'. Obviously, the ability to perform monitoring tasks requires an activated forebrain and thus depends on 'arousal'. Likewise, the 'arousing' consequences of novel, emotional, or stressful stimuli initiate and interact with attentional performance. However, the operational definition of sustained attention, and the measures generated to assess sustained attentional performance, are specific and dissociable from the concept of 'arousal'. While changes in 'arousal' typically are deduced from brain activity data (such as EEG data), an interpretation of data in terms of 'sustained attention' is necessarily based on behavioral performance data (e.g., detection rates, false alarm rates, etc.). As will be discussed further below, such a conceptual dissociation between arousal and sustained attention performance as well as the interactions between both constructs are supported by the organization of the neuronal circuits mediating these functions.

2.2. Sustained attention: variables and measures

2.2.1. Variables taxing sustained attention performance

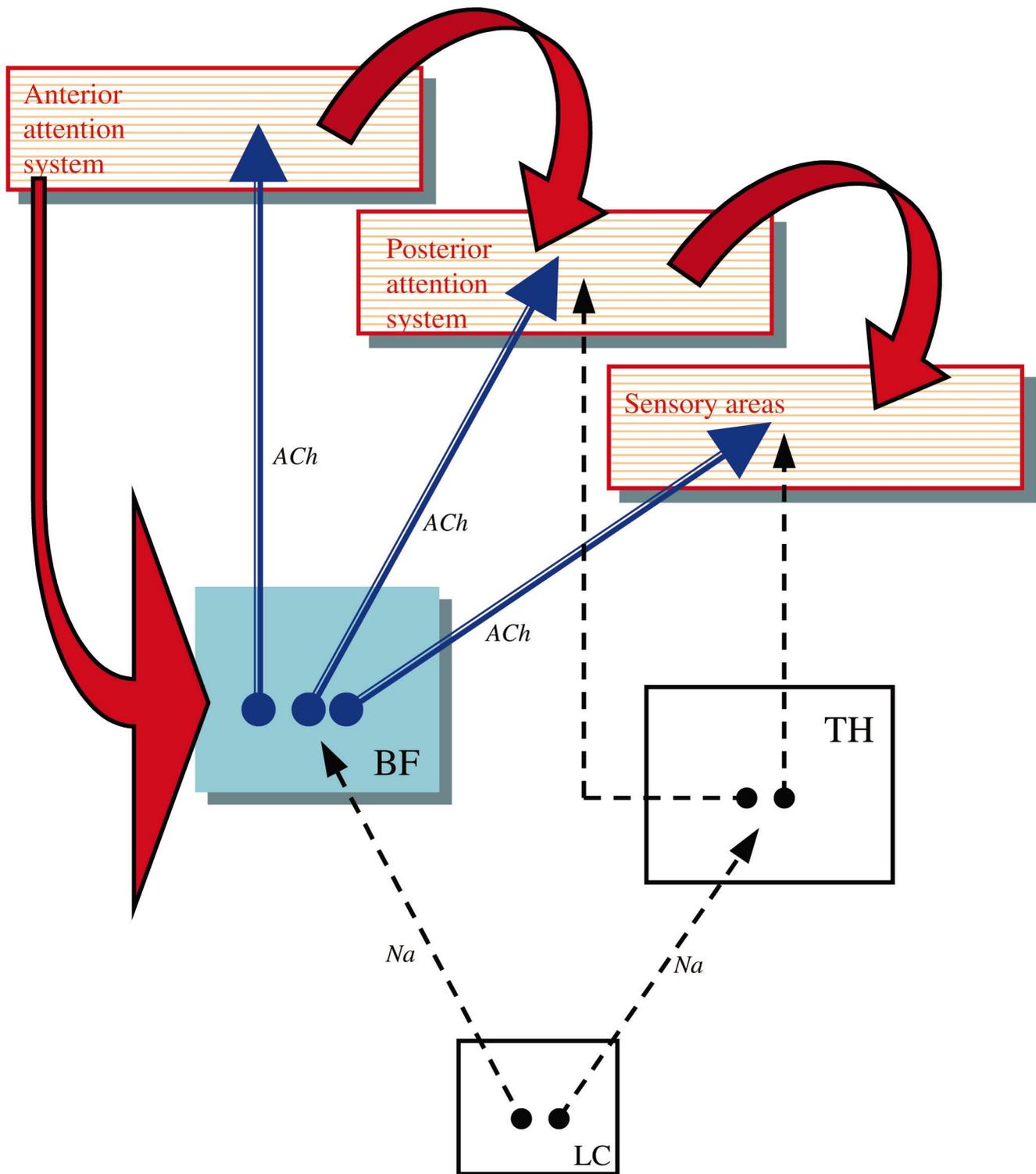Similar to other attentional capacities, the capacity to

Fig. 1. Schematic illustration of the major components of a neuronal network mediating sustained attention performance. The figure combines anatomical and functional relationships and represents a conceptual summary of the evidence from human neuropsychological and imaging studies and animal experimental approaches. Neuroimaging studies demonstrated consistent activation of right medial frontal and dorsolateral prefrontal cortical regions, as well as parietal cortical regions in subjects performing in sustained attention tasks. Activation of the 'anterior attention system' [75] has been suggested to modulate top-down the functions of posterior cortical areas, thereby enhancing and biasing sensory input processing in primary sensory through sensory-associational regions (curved arrows). Animal experiments determined the crucial role of cortical cholinergic inputs in sustained attention (ACh, acetylcholine). Activation of basal forebrain (BF) corticopetal cholinergic projections is necessary for sustained attention performance, and cortical cholinergic inputs may mediate, or at least critically contribute to, the activation of fronto-parietal regions. Furthermore, cholinergic inputs to the cortex mediate the facilitation of bottom-up sensory information processing. Activation of the cholinergic corticopetal projections represents a component of the top-down regulation associated with the recruitment of the anterior attention system (left arrow). The ability of 'arousal'-inducing stimuli to trigger attentional processing is mediated bottom-up largely via noradrenergic (Na) projections originating in the locus coeruleus (LC) and terminating in the thalamus (TH) and the basal forebrain.

sustain attention has been considered to represent a limited resource. Several variables have been demonstrated and conceptualized as taxing sustained attention performance [65,67]. (1) The successive (as opposed to the simultaneous) presentation of signal and non-signal features taxes sustained attention performance. (2) High event rate, that is the frequency of signal events, combined with unpredictability of the time of the presentation of the event (termed event asynchrony) and of the event type (e.g., signal vs. non-signal), enhances the demands on sustained attention performance. High event rates also represent a critical variable in the manifestation of a vigilance decrement. (3) Spatial uncertainty about the locus of event presentation also promotes the manifestation of vigilance decrements. (4) The use of dynamic (as opposed to static) stimuli, such as signals with variable luminance or duration also fosters the manifestation of a vigilance decrement, partly because the presentation of dynamic stimuli is associated with decreased discriminability. (5) Demands on working memory (as, for example, occurring in tasks with successive event presentation) tax sustained attention performance. (6) Using signals with conditioned or symbolic significance, thus requiring additional processing to report detection (as opposed to the pure detection of signals) is thought to foster the exhaustion of the sustained attention capacity. Such signals are considered to increase the demands for the 'controlled processing' of signals and thus to increase the allocation of resources consumed by the attentional task.

2.2.2. Practice

In experiments with human subjects, practice of sustained attention tasks typically is kept at a minimum in order to limit the degree to which task performance is mediated by highly automated attentional processing and to prevent the disappearance of the vigilance decrement [27]. Different levels of practice may account for a substantial proportion of conflicting data in the literature, and although the issue is widely recognized, the effects of practice on vigilance performance remain insufficiently investigated. Furthermore, extensive practice and the resulting high level of automatism may not necessarily decrease the demands on processing resources to the extent assumed in earlier theories. Conceptualizations of sustained attention as a process in which an 'attentional supervisory system' maintains target schemata that correspond with the actual detection requirements predict that the functions of this system consume processing resources even in well-practiced tasks, therefore producing performance decrements over time-on-task [95].

2.2.3. Reaction time versus number of detected signals and false alarms

In highly practiced vigilance tasks in which subjects exhibit high levels of detections of signals and low levels of false alarms, reaction time may become the critical measure of performance. Increased reaction times usually correlate with decreased detection rates, supporting the hypothesis that the former measure also indicates vigilance decrements. In humans, reaction times may increase several hundred milliseconds during monitoring tasks that last over an hour. In animals, reaction times have been analyzed and interpreted with great caution, specifically following manipulation of neuronal functions, as they are potentially confounded by a multitude of sensory and motor variables and competing behavioral activities.

2.2.4. Changes in sensitivity versus shift in criterion

Data generated by traditional vigilance tasks have been routinely analyzed using signal detection theory, to the extent that vigilance and signal detection theory have been considered interchangeable terms, and ignoring the fact that the latter in essence represents a statistical method. However, an analysis of sustained attention performance data using signal detection theory may provide the quantitative basis for interpreting changes in vigilance performance. Specifically, the number of signals detected is a combined result of signal detectability (or sensitivity) and the subject's criterion or 'willingness' to report detection of a signal. The former depends largely on the psychophysical characteristics of the signals relative to non-signals, while the latter is a more complex function of the subjects' general strategy, task instructions (e.g., performing in accordance with a conservative versus a risky criterion), and of task parameters such as cost/benefit considerations for reporting signals and false alarms. For example, a decline in the number of hits, that is the correct detection of signals, over a prolonged period of time may be due to an increasingly conservative criterion. Experimentally-induced increases in the probability for a signal typically result in a loosening of the criterion that is reflected by increases in hits and false alarms. Conversely, changes in performance in high event-rate, successive discrimination paradigms may be due rather to a decline in sensitivity. Signal detection theory-derived analyses potentially assist in dissociating the contribution of shifts in sensitivity and criterion to changes in vigilance performance [96].

3. Macroanatomical correlates

3.1. General interpretational issues

Macroanatomical correlates of sustained attention performance have been determined mainly by two lines of research. First, findings from neuropsychological studies have identified areas of brain damage or degeneration which are correlated with impairments in sustained attention performance. Second, and more recently, functional imaging studies have located areas in the intact brain in

which changes in metabolic activity correlate with sustained attention performance.

Complexities in the interpretation of brain damage in terms of determining the normal functions of the brain region of interest, although remaining a persistent topic in the literature, deserve continued and careful scrutiny. First, the functional consequences of the absence of a brain region routinely have been interpreted as indicating this area's functions in the intact brain, ignoring the more appropriate view that residual performance reflects the processing maintained by the residual brain. This interpretational concern arises in part from, and is further convoluted by, the often implicit conception of a particular brain region as a functionally distinct unit rather than representing a functionally critical node or intersection of multiple neuronal networks [25]. For example, the prominent (and seemingly compulsory) involvement of prefrontal cortical areas in diverse cognitive functions [8,21,92] may be associated with its central position within cortical associational, limbic and paralimbic neuronal networks rather than, or at least in addition to, the specific cognitive operations mediated via intra-prefrontal neuronal circuits [56].

The second interpretational issue concerns implicit assumptions underlying attempts to map complex cognitive functions onto brain structures. The prime issue concerns the assumption that the cognitive function of interest (e.g., sustained attention) represents a relevant functional unit that maps on, or is isomorphic with, a traditionally defined neuroanatomical region or neuronal system. Below, the converging evidence from neuropsychological and functional imaging studies, indicating that sustained attention maps onto macroanatomical structures such as the prefrontal cortex, with evidence from studies in animals, showing that neuronal manipulations of the activity of cholinergic inputs modulate sustained attention performance, is suggested to provide the basis for a description of the neuronal circuits mediating sustained attentional abilities.

3.2. Sustained attention following brain damage and neuronal degeneration

Damage to the frontal cortex as well as lesions in the (inferior) parietal lobe, result in decreases in the number of hits, increases in reaction time, and in the manifestation or augmentation of a decrement in sustained attention performance over time-on-task (e.g., Refs. [83,84]). The detrimental effects of distractors on sustained attention performance appear to be particularly prominent in patients with right frontal lobe damage, while the performance of patients with parietal lesions generally is more sensitive to the effects of high event rates (but see Ref. [3]). The specificity of interpretations of the effects of right fronto-parietal damage in terms of impairments in sustained attention [81] has been supported by studies which excluded the possibility that increased fatigue, differential

effects of practice, or differences in motivational processes significantly confound impairments in vigilance performance in these patients [29].

Aged humans and, more dramatically, patients with age-related dementias exhibit lower detection rates in continuous performance tasks and other standard neuropsychological tests that assess an insufficiently defined blend of arousal and vigilance functions. As the majority of the available studies conducted in patients with Alzheimer's disease did not selectively assess sustained attention [66], the reliability of demonstrating a vigilance decrement in these patients has remained unsettled. Most likely, the demonstration of such effects depends on the degree to which tasks demand the sustained and effortful monitoring and processing of stimuli, thereby presumably taxing fronto-parietal functions. Likewise, the extent to which impairments in sustained attention can be demonstrated, similar to impairments in selective and divided attention, in early stages in Alzheimer's disease, is unclear [71]. In general, however, the assumptions about the neurobiological bases for the attentional impairments in Alzheimer's disease, including the decline in sustained attention, have generally followed the fronto-parietal conceptualizations of attentional functions and thus attributed impairments to prefrontal dysfunction [66], despite these patients having more widespread damage that includes parietal cortical and subcortical, specifically basal forebrain, regions.

3.3. Evidence from functional neuroimaging studies

The extent to which evidence from lesion studies and functional imaging studies agree is remarkable. Anterior cingulate and dorsolateral prefrontal as well as parietal cortical regions, located primarily but not exclusively in the right hemisphere, have been consistently found to be activated in subjects performing sustained attention tasks, irrespective of the modality of stimuli used in these tasks [11,13,26,68]. Furthermore, a decline in activity in fronto-parietal–temporal regions over the course of task performance has been suggested to mediate vigilance decrements [16,69].

In addition to the modality-independent activation of right fronto-parietal regions during sustained attention, demands on monitoring and discriminating stimuli of a particular modality necessarily activate sensory cortical regions as well as sensory associational areas [12,26]. Collectively, the findings from functional imaging studies have supported a general model that describes sustained attention as a 'top-down' process that begins with the subject's general readiness to detect and discriminate information, mediated largely via right fronto-parietal regions, and which enhances the perceptual and spatial processes that contribute to sustained attention performance via activation of posterior parietal areas and facilitation of the processing of sensory inputs in primary and

secondary sensory and sensory-associational regions ([39,46]; see also the discussion in Refs. [13,75]). This concept of a top-down facilitation of perceptual components of attentional processes corresponds with the increases in responsiveness and selectivity of single cell firing activity observed in sensory associational areas under conditions of increased demands on attention [18].

4. Neuronal circuits mediating sustained attention performance

Evidence from studies designed to manipulate the functioning of defined neuronal circuits and assess the consequences for attentional performance, or to record from neurons constituting such circuits in animals performing in attentional tasks, is expected to explain the prominent role attributed to frontal cortical and parietal regions in human neuropsychological and functional imaging studies. Such reductionist explanations are also expected to specify the nature of the processing mediated via fronto-parietal cortical areas in sustained attention, and to determine the specific neuronal circuits responsible for the activation of these areas observed in imaging studies or for the impairments in sustained attention resulting from damage or degenerative processes in these areas. Although the focus of the present discussion is on the neuronal mechanisms mediating sustained attention in the human brain, evidence from animal experimental approaches therefore represents a necessary component of such an analysis.

4.1. Animal behavioral tests of sustained attention

Animal experimental approaches to the study of the neuronal mechanisms of attention only recently have become viable as tasks for the measurement of different aspects of attention became available. These tasks were designed and demonstrated to be valid in accordance with the criteria constituting the psychological construct (above). Two tasks for use in rats have been extensively used for the study of sustained attention. First, Robbins, Everitt, and co-workers (e.g., Ref. [78]) employed the '5-choice serial reaction time task' that requires animals to monitor the location of a briefly presented light in one out of five spatially arranged target areas. This task combines aspects of the continuous performance tasks used in human studies and primarily tests sustained spatial attention. Second, an operant task requiring rats to detect signals and to discriminate between signals and non-signals was designed to generate a complete set of response categories (hits, misses, false alarms, correct rejections). Importantly, a false alarm in this task represents a discrete 'claim' for a signal in a non-signal trial, therefore overcoming the limitations of the response rate-confounded calculation of false alarm rates in more traditional signal detection tasks

used in animal research. The impact of parametric manipulations of task variables, distractors, event rate, or the probability for signals supports the validity of the measures of performance generate by this task in terms of indicating sustained attention ([52]; for a version of this task used in humans see Ref. [48]). Similar to tasks used in human research, significant vigilance decrements in intact animals were not always reliably observed, but usually emerged in interaction with detrimental neuronal manipulations (see below).

4.2. Basal forebrain corticopetal cholinergic projections: a necessary component of the neuronal circuits mediating sustained attention

The basal forebrain corticopetal cholinergic projections terminate in practically all areas and layers of the cortex (for review see Ref. [87]). For several decades, human and animal psychopharmacological experiments on the effects of nicotine and muscarinic receptor antagonists (such as scopolamine and atropine) have strongly implicated cholinergic systems in sustained attention. Beginning with the demonstration of the effects of excitotoxic lesions of the basal forebrain on rats' performance in the five-choice reaction time and other tasks and on the performance of monkeys in a version of Posner's overt orientation task (e.g., Refs. [7,59,79,102]), the crucial dependency of attentional abilities on the integrity of this system has been extensively explored. Collectively, the available evidence from studies on the effects of loss of cortical cholinergic inputs demonstrates the following: (1) selective lesions of the basal forebrain corticopetal cholinergic projections, produced by infusions of the cholinoimmunotoxin 192 IgG-saporin into the region of the nucleus basalis of Meynert and the substantia innominata in the basal forebrain, are sufficient to produce profound impairments in sustained attention [50]. (2) The lesion-induced impairment in performance is restricted to signal trials while correct rejections remain unaffected, reflecting the absence of the normally augmenting effects of cortical acetylcholine (ACh) on the processing of sensory inputs (e.g., Refs. [54,62,98,103]. Moreover, such lesions decrease the vigilance levels and augment the vigilance decrement [50]. (3) Loss of cortical cholinergic inputs alone, as opposed to loss of all basal forebrain cholinergic efferents, suffices to produce such impairments [53]. (4) The impairments in sustained attention observed following cortical cholinergic deafferentation are persistent and do not recover, even following extended periods of daily practice of performance [50]. (5) The extent of the impairments in sustained attention is tightly correlated with the degree of loss of cortical cholinergic inputs, particularly in fronto–dorsal cortical areas [50].

Evidence from studies designed to manipulate the excitability of basal forebrain corticopetal cholinergic projections confirmed the crucial role in cortical choliner-

gic inputs in sustained attention performance. For example, infusions of positive or negative modulators of GABAergic (GABA; γ-aminobutyric acid) transmission into the basal forebrain, that augment or decrease, respectively, the ability of GABA to inhibit the excitability of corticopetal cholinergic projections [58,86], bidirectionally alter sustained attention performance. Specifically, augmentation of GABAergic inhibition in the basal forebrain of rats trained in a sustained attention task produced transient lesion-like effects characterized by a selective decrease in the animals' ability to detect visual signals. Conversely, infusions of a negative GABA-modulator into the basal forebrain increased the number of false alarms, that is the number of 'claims' for signals in non-signal trials [38]. The latter effect can be interpreted as reflecting an abnormal over-processing of the stimulus situation, mediated via disinhibition of cortical cholinergic inputs. Likewise, infusions of an antagonist for glutamatergic NMDA receptors (APV) into the basal forebrain produce effects on sustained attention performance that resemble those of cholinergic lesions or of positive GABA modulators. Conversely, infusions of NMDA, which augment cortical ACh release [24], resulted in an increase in false alarms similar to those produced by a negative GABA modulator [100]. These and other data have consistently supported the hypothesis that modulation of the activity of cortical cholinergic inputs mediate changes in performance in sustained attention [87].

The focus on cortical cholinergic inputs in the mediation of sustained attention is not based solely on the effects of lesions or of manipulation of the excitability of corticopetal projections. Recent studies demonstrated that ACh release in the cortex in animals performing a sustained attention task is correlated with demands on sustained attention [36]. While increased cortical ACh release was associated generally with attentional task performance, recovery of performance following the presentation of a visual distractor was distinctively associated with increases in ACh release. Furthermore, performance of simple operant procedures controlling for the effects of lever presses for food reward, movement in the operant chambers and the presentation of visual stimuli was not associated with increases in cortical ACh release [35].

The hypothesis that distractor-induced increases in the demands for sustained attention are mediated via cortical cholinergic inputs has also been supported by neurophysiological evidence. Single neuron recording studies in the medial prefrontal cortex (mPFC) revealed that mPFC neurons are engaged in multiple aspects of sustained attention performance, including response and reward rate [31]. Importantly, the baseline level of spontaneous activity in a defined population of mPFC neurons systematically increased when a visual distractor was present during attentional performance. In the current context, this distractor-induced increase in mPFC neural activity is hypothesized, in a top-down fashion, to enhance the processing of

sensory inputs in other more posterior cortical areas. Furthermore, glutamatergic projections from the prefrontal cortex to the basal forebrain [107] contribute to the activation of basal forebrain corticopetal projections [24]. Thus, this prefrontal–basal forebrain–cortex circuit represents a component of the PFC-controlled top-down effects, collectively functioning to bias the subject toward the specific attentional demands at hand (see below for further discussion). Critical support for the role of acetylcholine in this modulation of attention comes from the observation that the distractor-induced increases in mPFC unit firing were no longer observed following unilateral cholinergic deafferentation restricted to the recording area ([31]; Fig. 2).

The absence of distractor-induced increases in spontaneous activity of mPFC neurons following local cholinergic deafferentation of the recording area suggests that the cholinergic input to these neurons enhances their excitability. According to present hypotheses, when a visual distractor is introduced during task performance, the basal forebrain cholinergic system becomes activated in proportion to the level of attention required to maintain performance (see also Ref. [47]), which subsequently leads to increased unit firing in those neurons most tightly coupled to the cholinergic afferents, either directly or through local synaptic interactions. Alternatively, the increase in activity can be thought of not as being driven, but rather as 'monitoring' the level of basal forebrain activation. When the basal forebrain is activated, under conditions of high attentional demand, a subset of neurons in the mPFC detect this change and elevate their activity and subsequently project this enhanced activity to the posterior cortical regions to modulate the processing of signals.

The loss of distractor-induced increases in unit activity following cholinergic deafferentation of the recording area is not confounded by alterations in behavioral performance as evidenced by the fact that the restricted, unilateral deafferentation of mPFC cholinergic inputs had no effect on sustained attentional performance. In other words, the loss of distractor-induced increases in unit activity is solely attributed to the loss of cholinergic input to the region of the recorded neurons. The lack of attentional effects of the restricted cholinergic deafferentation should not be taken to indicate that this region of cortex is not critically dependent on cholinergic input for attentional performance. On the contrary, bilateral medial prefrontal cholinergic deafferentation, produced by bilateral infusions of 192 IgG-saporin into the mPFC, resulted in highly selective impairments in sustained attention, that is a loss of signal detection accuracy during the presence of a visual distractor, but not under standard attentional conditions [30].

The lack of effect of bilateral mPFC cholinergic deafferentation on performance under standard attentional conditions suggests that mPFC cholinergic inputs may have less of a role in enhancing signal detection and more of a role in filtering out the distractor. Thus, prefrontal

Before Cholinergic Deafferentation

After Cholinergic Deafferentation

Distractor
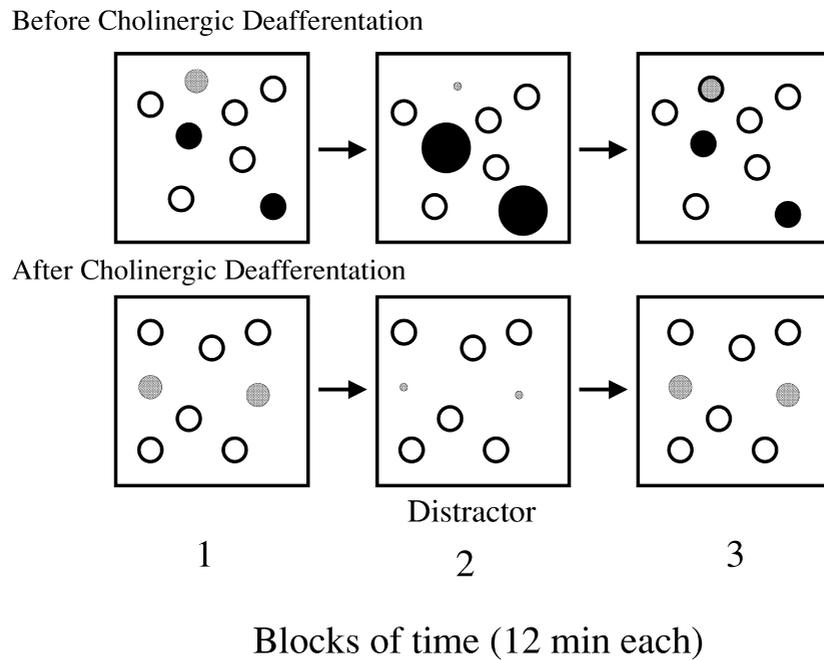
1
2
3

Blocks of time (12 min each)

Fig. 2. Representation of attentional correlates of neural activity in the medial prefrontal cortex (mPFC) before and after local cholinergic deafferentation during the presence (block 2) or absence (blocks 1 and 3) of a visual distractor. Each circle represents a single pyramidal neuron with its size indicating its rate of activity. Three types of neurons, defined post-hoc, are shown: those that increase (black), decrease (gray) or do not change (white) activity in the presence of the distractor. Prior to the cholinergic lesion, a population of neurons (black circles) displays distractor-induced increases in activity and a smaller population show distractor-induced decreases (gray circles). After the cholinergic lesion, neurons with distractor-induced increases are no longer observed, and there is a doubling of the proportion of neurons with distractor-induced decreases. The loss of distractor-induced increases following deafferentation indicates the importance of basal forebrain cholinergic afferents in the attentional modulation of the mPFC.

circuits may contribute to signal processing by modulating the transfer of sensory information in posterior cortex and by suppressing distracting sensory information. Both the distractor-suppressing and signal-enhancing functions are supported by, and in fact depend on, proper cholinergic stimulation in all cortical areas mediating these functions, and such cholinergic stimulation is maintained in part by the direct feedback from the mPFC to the basal forebrain (see Fig. 1). Moreover, as increases in cortical ACh release are associated with standard task performance, and specifically with the increased attentional efforts supporting the recovery of performance following the presentation of a distractor [36], the available data collectively suggest that the integrity of mPFC cholinergic inputs is necessary for sustained attentional performance under the condition of distractor-induced increases in demands on attentional processing. In contrast, cholinergic inputs to specifically the mPFC are not necessary for standard sustained attention performance, but the integrity of cholinergic inputs to greater parts of the cortex is necessary for such performance [50]. This dissociation further supports the dual functions mediated via an activated basal forebrain corticopetal cholinergic projection system, that is contributing to the activation of the prefrontal cortex which is crucial for filtering distractors and recruiting top-down processes and, simultaneously, interacting with bottom-up processes

to gate and enhance the processing of sensory inputs at all levels of cortical input processing (Fig. 1).

Furthermore, the same mPFC neurons that are thought to modulate or bias signal processing in posterior cortical sites are simultaneously engaged in the reward and response aspects of task performance, and their response characteristics do not change as a function of attentional demand ([31]; see also Ref. [91]). Thus, the presence of the visual distractor, which resulted in more demanding attentional conditions and produced deficits in signal detection accuracy, did not alter the behavioral correlates of unit activity indicating that the mPFC is engaged in both cognitive and non-cognitive components of performance. This observation suggests that, in the mPFC, the function of cholinergic inputs to filter distractors and to mediate general operant performance may also be differentiated. Future studies need to be designed to distinguish further between, and to gauge the relative contributions of, these two components of the effects of activated cortical cholinergic inputs to the mPFC and the entire cortex.

4.3. Afferent and efferent components of the corticopetal cholinergic system

The hypothesis that sustained attention performance is mediated by cholinergic inputs to widespread areas of the

cortex implies that cholinergic inputs are not 'pre-wired' for all possible stimuli, and that cortical ACh-mediated enhancement of the processing of sensory and association-al information occurs in a rather cortex-wide fashion. Furthermore, cognitive/behavioral specificity of the effects of ACh is hypothesized to result from interactions with other, converging (e.g., thalamic and associational) inputs (for more discussion see Ref. [87]). For example, ACh-mediated increases in the responsivity of auditory cortical neurons to stimuli, the enhancement of the auditory response selectivity of these neurons and, generally, ACh-mediated facilitation of the detection and discrimination of auditory inputs, are due to interactions between activated cortical cholinergic and thalamic inputs converging in the auditory cortex [104]. In the visual cortex, evidence in support of a cholinergically-mediated enhancement of intralaminar transfer of information between cortical col-umns suggest that the effects of ACh in sensory areas go beyond facilitation of sensory inputs and include enhance-ment of higher perceptual processes [43,106]. Compared to the effects of ACh in sensory cortex, information about the effects of ACh on the firing properties of individual neurons in associational areas is scarce. Generally, ACh produces a complex combination of effects on the ex-citability of cortical interneurons and efferent projections which, collectively, acts to enhance the ability of cortical neurons to process subcortical or associational inputs [33], and thus the processing of conditioned or behaviorally significant stimuli. Thus, the distractor-associated, cholinergically-mediated changes in prefrontal neuronal activity (above) presumably reflect the interactions be-tween increases in the activity of cholinergic inputs to these areas [36] and the rule-based processing of the stimulus situation mediated via prefrontal circuits and associated top-down processes (e.g., Refs. [20,49,57,82,105]). What then regulates the activation of the cortical cholinergic input system in such situations, thereby facilitating attentional performance?

In general terms, the limbic and cortical afferent projec-tions of basal forebrain neurons 'provide' information about the behavioral significance of stimuli based on previous experience, motivation, and behavioral context [91]. This hypothesis has been extensively substantiated with respect to basal forebrain afferent projections arising from nucleus accumbens; furthermore, the available litera-ture indicates close interactions between amygdaloid–ac-cumbens circuits [23,34] which, collectively, 'import' information about the motivational and affective quality of stimuli to basal forebrain neurons [89]. Such afferent information is integrated in the basal forebrain with the converging input from the prefrontal cortex [107] that, as discussed above, recruits basal forebrain corticopetal pro-jections as a component of the top-down regulation of neuronal systems mediating attentional performance.

The attentional effects of excitotoxic lesions of the mPFC, that is lesions which destroy the efferent projec-tions of this area, provide initial insight into the functional power of such top-down processes. Obviously, the effects of such lesions go beyond specific attentional conse-quences and include a wide range of fundamental be-havioral and cognitive impairments, particularly executive functions (e.g., Refs. [20,60,80]). In animals tested in the same sustained attention task that was used to deduce the role of cortical cholinergic inputs (above), excitotoxic lesions of the mPFC resulted in robust impairments in performance which did not specifically reflect impairments in sustained attention but indicated a randomization of response selection, reflecting a disruption of fundamental executive processes. Moreover, the lesioned animals' performance was insensitive to the effects of a distractor [57]. Thus, the neuronal circuits that are *selectively* mediating sustained attention performance may be re-stricted to the cortical cholinergic input system and its afferent sources, as already concluded above. The top-down processes mediated via frontal efferent projections clearly are crucial for proper sustained attention perform-ance, but their integrity is not exclusively important for sustained attention performance. To the extent that the attentional effects of activation of cholinergic inputs to the mPFC, or of cholinergic deafferentation of this area, can be interpreted in terms of ACh-dependent top-down pro-cesses, such processes may be more restricted than those deduced from the attentional effects of excitotoxic lesions of the mPFC, and they may function specifically to cope with the increased demands on sustained attention per-formance caused by distractors.

The enhanced processing of information in sensory cortical areas represents an interaction between the top-down regulation of these areas by the 'anterior attention system' and the direct effects of ACh in the cortex. Activation of cortical cholinergic inputs mediates two synergistically interacting processes, namely the activation of the 'anterior attention system' and thus the activation of the top-down functions of this system and the enhancement of sensory information processing in sensory and sensory-associational areas via activation of cholinergic inputs (see Fig. 1). As activation of the basal forebrain corticopetal cholinergic system itself is conceptualized as a component of the top-down processes, it is important to understand that there is no evidence in support of a sequential recruitment of the PFC and basal forebrain; rather, the close interactions between prefrontal regions and the basal forebrain, based anatomically on a closed-circuit (above), necessarily mediates the activation of the 'anterior atten-tion system'. The exception from this hypothesis are situations in which arousal-induced attentional processes (e.g., by stressful or anxiogenic stimuli; [4]) are mediated 'bottom-up' by LC ascending projections to recruit fore-brain attentional circuits (above). In such situations, the basal forebrain corticopetal cholinergic projections may mediate the activation of the prefrontal cortex to trigger attentional processing (see also Ref. [94]).

In the aggregate, the ACh-mediated effects in the cortex facilitate the subject's readiness to monitor source(s) of signals, to detect such signals even if they occur rarely and unpredictably, to initiate the cognitive processes that result in a decision for, and the execution of, a response that indicates detection and processing of a signal, and to filter distractors. The data by McGaughy et al. [50] further substantiate this conceptualization as lesions of cortical cholinergic inputs selectively impaired the animals' ability to detect signals but not to reject non-signals. The rejection of non-signals does not depend on ACh-mediated enhancement of converging sensory inputs and thus, this measure does not reveal the absence of the interactions between ACh-activated top-down processes and ACh-facilitated sensory processing in lesioned animals. Conversely, such lesions disrupted the detection of signals because this required the ACh-mediated enhancement of sensory inputs, which was disrupted by the lesion.

The model illustrated in Fig. 1 also predicts that loss of cholinergic inputs that is restricted to the primary and secondary visual cortical areas does not suffice in impairing visual sustained attention performance [37]. To reiterate, the present model stresses that sustained attention performance depends on the interactions between the ACh-induced enhancement of sensory input processing throughout all levels of cortical input processing and the ACh-mediated recruitment of top-down processes via frontal cortical regions. Thus, restricted lack of ACh-mediated enhancement of primary and secondary visual input processing, although clearly affecting the neurophysiological correlates of visual information processing [32,43,90,106] would not be expected to affect sustained attention performance. The absence of attentional effects of infusions of the cholinotoxin 192 IgG-saporin into the primary and secondary visual cortex [37] also supports the notion that performance in such a task cannot be attributed solely to the ACh-mediated enhancement of the primary processing of sensory stimuli serving as targets in this task.

Finally, the prevailing focus on the cholinergic system in sustained attention should not be confused with the suggestion that sustained attention would be 'localized' within this neuronal system. Rather, the anatomical and electrophysiological characteristics of this neuronal system make it an ideal mechanisms for gating information processing in the entire cortical mantle [56]. Thus, in terms of localizing sustained attention, sustained attention is more adequately described as being mediated via the activation of the cortex by cholinergic inputs, specifically of anterior-parietal circuits, and the interactions between the modulation of sensory processing by the top-down processes, including the recruitment of interhemispheric circuits, the direct cholinergic stimulation of sensory areas and thalamic input to these regions (Fig. 1). Thalamic inputs import sensory information and, when activated via noradrenergic afferents, contribute to the induction of 'arousal' that is a prerequisite for proper attentional

performance (above). Thus, sustained attention is a function based on distributed, parallel circuits, with the cortical cholinergic inputs representing a crucial link in the mediation of sustained attention.

5. Ascending noradrenergic projections: the 'arousal' link?

The basis for the conceptual dissociation between sustained attention and arousal is stressed above. In support of this dissociation, the findings from functional neuroimaging studies have suggested that the neuronal circuits mediating the necessary arousal for proper sustained attention performance differ from those correlated with sustained attention. Specifically, the arousal components may be mediated via activation of the thalamus. Attentional performance-associated increases in thalamic activity were observed under low arousal conditions, possibly reflecting the mechanisms mediating the increased attentional effort required to perform the task under low arousal conditions ([72], see also the discussion in Ref. [13]).

Although noradrenergic projections originating from the locus coeruleus (LC) have been traditionally considered to mediate increases in arousal and aspects of attentional processing, their specific roles in sustained attention and arousal, respectively, have remained less well defined. Psychopharmacological studies in humans and in animals traditionally did not dissociate between arousal and attention when interpreting the effects of systemic manipulations of noradrenergic neurotransmission, particularly the effects of the administration of the α_2 receptor agonist clonidine. However, the findings from more recent studies support the hypothesis that rather than mediating specific attentional functions, ascending noradrenergic projections regulate the more general activation or arousal of the forebrain that is required for proper sustained attention performance [15,72]. Such a noradrenergically-mediated role in attentional performance may be attributed primarily to thalamic mechanisms. Coull and co-workers demonstrated that the administration of clonidine in humans performing a rapid visual information processing task resulted in the reduction of thalamic activity at baseline but not during performance [13–15]. The data from these studies collectively support the hypotheses that the attentional effects of clonidine depend more on the state of arousal than revealing a primary noradrenergic component mediating sustained attention, and that thalamic circuits mediate the interactions between arousal and attention (see also Ref. [69]).

Aston-Jones et al. developed a comprehensive model of the noradrenergic contributions to attentional processes. Based largely on the sympatho–excitatory afferents of the LC, noradrenergic projections are proposed to serve as the cognitive limb of a 'rapid response system' acting 'bottom-

up' to recruit telencephalic systems mediating attentional processes [2]. For example, the privileged attentional processing of fear- and anxiety-related stimuli has been theorized to depend on the noradrenergic activation of basal forebrain corticopetal projections [4]. Evidence in support of a regulation of the LC excitability by the prefrontal cortex indicates that even in such situations, bottom-up processes do not act in an isolated fashion but are subject to 'top-down' control [40]. Collectively, this hypothesis suggests that attentional functions are triggered, but not mediated, by noradrenergic ascending activation, and that sustained attention performance may not critically depend on variations in activity in ascending noradrenergic projections (see also Ref. [77]). This hypothesis is also supported by the results from several studies indicating that the ascending noradrenergic system does not crucially mediate attentional performance unless the state of arousal is manipulated by the presentation of salient, novel, or stressful stimuli [5,9,28,51].

6. Relationships with other forms of attention

Given the close theoretical relationships between different aspects of attention (sustained, selective, divided), it should not come as a surprise that the available data from neuropsychological, functional imaging, and animal experimental studies already suggest extensive overlaps in the circuits mediating different aspects of attention (e.g., Refs. [1,6,8,10,13,42,59,99,101]). For research purposes, it is important to maintain clear definitions of the aspects of attention studied. However, with respect to real-life performance, and to the underlying brain mechanisms, those differentiations may be of more limited significance. Monitoring a particular source of information requires, at the same time, the selection of such a source and the rejection of competing sources, and the allocation of processing resources to this task. Obviously, such tasks cannot be performed without mnemonic processing, taxing additional executive functions. Likewise, impairments in attention are difficult to be conceived as remaining restricted to a particular aspect of attention, particularly as such impairments escalate and affect all cognitive abilities [88]. Thus, the present reductionist attempt to determine the neuronal circuits mediating specifically sustained attentional functions represents a first step toward a more comprehensive understanding of the multiple circuits that allow us to effectively attend to our internal and external environment.

7. Major unresolved issues

The hypotheses that the activation of the fronto-parietal areas observed in humans performing sustained attention tasks reflects in part the consequences of cholinergic

stimulation of these regions is attractive but remains unsubstantiated. The present model predicts more widespread areas of cortical activation than reported in most of the available studies, although the relatively selective activity changes reported in those studies may in part be due to the methods used to isolate regions of interest in such studies [85]. Furthermore, the predominant role of the right hemisphere for sustained attention observed in human studies has not been addressed in the animal experimental literature on the functions of cortical cholinergic inputs. Right cortical lesions produce a more severe sensory neglect in humans and rats than left lesions [44,55], and lateralized cortical muscarinic receptor densities have been reported [70], raising the possibility that the prominent right hemispheric involvement in sustained attention is associated with lateralized cholinergic function [7]. It is also possible that in patients with lateralized lesions, sustained attention performance involves greater demands on alertness and thus on ascending noradrenergic activity. To the extent that noradrenergic inputs to the cortex are asymmetric and right hemisphere-dominant, patients with lesions in right fronto-parietal areas would be more susceptible to attentional challenges [73,81]. Alternatively, evidence in support of a cortical lateralization of sustained attention may be associated with the type of tasks used. This speculation predicts that spatial, non-verbal sustained attention tasks by default foster the demonstration of right hemispheric dominance in the mediation of sustained attention. As radiotracers for the visualization of presynaptic cholinergic activity and muscarinic and nicotinic receptor stimulation are becoming available for human SPECT and PET studies (e.g., Refs. [45,61,64]), future experiments will be capable of testing the hypothesis that sustained attention performance is associated specifically with increases in cholinergic transmission in the cortex.

8. Conclusions

Sustained attention represents a fundamental component of the cognitive capacities of humans. Aberrations in the ability to monitor significant sources of information rapidly develop into major cognitive impairments. Human neuropsychological and functional imaging studies have pointed to fronto-parietal areas, particularly in the right hemisphere, as being prominently involved in the mediation of sustained attention, or vigilance. Animal experimental evidence strongly supports the basal forebrain corticopetal cholinergic projection as a major component of the neuronal circuits mediating sustained attention performance. Activation of corticopetal cholinergic projections contributes to the recruitment of the anterior attention system and the associated top-down regulation of sensory and sensory-associational processing and, directly, enhances sensory input processing mediated via cholinergic projections to sensory cortical regions. These dual and interact-

ing functions of cortical ACh represent the crucial neuronal mechanisms mediating sustained attentional abilities. Future research will test these hypotheses in humans by using PET combined with radiotracers for markers of cholinergic transmission and muscarinic and nicotinic receptor function. Furthermore, animal models on the long-term attentional and cognitive effects of changes in cortical cholinergic inputs are needed. Finally, while hypotheses about the attentional consequences of loss of corticopetal cholinergic neurons or of decreases in cortical cholinergic transmission have been extensively studied, little is known about the long-term attentional consequences of pathological processes that are associated with abnormal increases in the (re)activity of cortical cholinergic inputs [88].

Acknowledgements

References

[1] R.A. Adcock, R.T. Constable, J.C. Gore, P.S. Goldman-Rakic, Functional neuroanatomy of executive processes involved in dual-task performance, Proc. Natl. Acad. Sci. 97 (2000) 3567–3572.

[2] G. Aston-Jones, J. Rajkowksi, P. Kubiak, R.J. Valentino, M.T. Shipley, Role of locus coeruleus in emotional activation, Prog. Brain Res. 107 (1996) 379–402.

[3] T. Audet, L. Mercier, S. Collard, A. Rochette, R. Hébert, Attention deficits: is there a right hemisphere specialization for simple reaction time, sustained attention, and phasic alertness?, Brain Cogn. 43 (2000) 17–21.

[4] G.G. Berntson, M. Sarter, J.T. Cacioppo, Anxiety and cardiovascular reactivity: the basal forebrain cholinergic link, Behav. Brain Res. 94 (1998) 225–248.

[5] S. Birnbaum, K.T. Gobeske, J. Auerbach, J.R. Taylor, A.F.T. Arnsten, A role for norepinephrine in stress-induced cognitive deficits: α-1-adrenoceptor mediation in the prefrontal cortex, Biol. Psychiatry 46 (1999) 1266–1274.

[6] D.J. Bucci, P.C. Holland, M. Gallagher, Removal or cholinergic input to rat posterior parietal cortex disrupts incremental processing of conditioned stimuli, J. Neurosci. 18 (1998) 8038–8046.

[7] P.J. Bushnell, A.A. Chiba, W.M. Oshiro, Effects of unilateral removal of basal forebrain cholinergic neurons on cued target detection in rats, Behav. Brain Res. 90 (1998) 57–71.

[8] R. Cabeza, L. Nyberg, Imaging cognition II: an empirical review of 275 PET and fMRI studies, J. Cogn. Neurosci. 12 (2000) 1–47.

[9] M. Carli, T.W. Robbins, J.L. Evenden, B.J. Everitt, Effects of lesions of ascending noradrenergic neurons on performance of a 5-choice serial reaction time task in rats: implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal, Behav. Brain Res. 9 (1983) 361–380.

[10] A.A. Chiba, D.J. Bucci, P.C. Holland, M. Gallagher, Basal forebrain cholinergic lesions disrupt increments but not decrements in conditioned stimulus processing, J. Neurosci. 15 (1995) 7315–7322.

[11] R.M. Cohen, W.E. Semple, M. Gross, A.C. King, T.E. Nordahl, Metabolic brain pattern of sustained auditory attention, Exp. Brain Res. 92 (1992) 165–172.

[12] M. Corbetta, F.M. Miezin, S. Dobmeyer, G.L. Shulman, S.E. Petersen, Attentional modulation of neuronal processing of shape, color, and velocity in humans, Science 248 (1990) 1556–1559.

[13] J.T. Coull, Neural correlates of attention and arousal: insights from electrophysiological, functional neuroimaging and psychopharmacology, Prog. Neurobiol. 55 (1998) 343–361.

[14] J.T. Coull, C.D. Frith, R.J. Dolan, R.S.J. Frackowiak, P.M. Grasby, The neural correlates of the noradrenergic modulation of human attention, arousal and learning, Eur. J. Neurosci. 9 (1997) 589–598.

[15] J.T. Coull, R.S.J. Frackowiak, C.D. Frith, Monitoring for target objects: activation of right frontal and parietal cortices with increasing time on task, Neuropsychology 36 (1998) 1325–1334.

[16] J.T. Coull, C.D. Frith, R.S.J. Frackowiak, P.M. Grasby, A fronto-parietal network for rapid visual information processing: a PET study of sustained attention and working memory, Neuropsychology 34 (1998) 1085–1095.

[17] N. Cowan, Attention and Memory: An Integrated Framework, Oxford University Press, New York, 1995.

[18] R. Desimone, Neural mechanisms for visual memory and their role in attention, PNAS 93 (1996) 13494–13499.

[19] R. Desimone, J. Duncan, Neural mechanisms of selective visual attention, Annu. Rev. Neurosci. 18 (1995) 193–222.

[20] R. Dias, T.W. Robbins, A.C. Roberts, Dissociation in prefrontal cortex of affective and attentional shifts, Nature 380 (1996) 69–72.

[21] J. Duncan, R.J. Seitz, J. Kolodny, D. Bor, H. Herzog, A. Ahmed, F.N. Newell, H. Emslie, A neural basis for general intelligence, Science 289 (2000) 457–460.

[22] H.E. Egeth, S. Yantis, Visual attention: control, representation, and time course, Annu. Rev. Psychol. 48 (1997) 269–297.

[23] B.J. Everitt, M. Cador, T.W. Robbins, Interactions between the amygdala and ventral striatum in stimulus–reward associations: studies using a second order schedule of sexual reinforcement, Neuroscience 30 (1989) 63–75.

[24] J. Fadel, M. Sarter, J.P. Bruno, Basal forebrain glutamatergic modulation of cortical acetylcholine release, Synapse (2001) in press.

[25] M.J. Farah, Neuropsychological inference with an interactive brain: a critique of the 'locality' assumption, Behav. Brain Sci. 17 (1994) 43–104.

[26] G.R. Fink, P.W. Halligan, J.C. Marshall, C.D. Frith, R.S.J. Frackowiak, R.J. Dolan, Neural mechanisms involved in the processing of global and local aspects of hierarchically organized visual stimuli, Brain 120 (1997) 1779–1791.

[27] A.D. Fisk, M.W. Scerbo, Automatic and controlled processing approach to interpreting vigilance performance: a review and reevaluation, Hum. Factors 29 (1987) 653–660.

[28] S.L. Foote, G. Aston-Jones, F.E. Bloom, Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal, PNAS 77 (1980) 3033–3037.

[29] O. Godefroy, M. Cabaret, M. Rousseaux, Vigilance and effects of fatigability, practice and motivation on simple reaction time tests in patients with lesions of the frontal lobe, Neuropsychology 32 (1994) 983–990.

[30] T.M. Gill, J. Masters, M. Sarter, B. Givens, The role of acetylcholine within the medial prefrontal and posterior parietal cortices during sustained visual attention in the rat, Soc. Neurosci. Abstr. 25 (1999) 1895.

[31] T.M. Gill, M. Sarter, B. Givens, Sustained visual attentional performance-associated prefrontal neuronal activity: evidence for cholinergic modulation, J. Neurosci. 20 (2000) 4745–4757.

[32] T.H. Harding, R.W. Wiley, A.W. Kirby, A cholinergic-sensitive channel in the cat visual system tuned to low spatial frequencies, Science 221 (1983) 1076–1078.

[33] M.E. Hasselmo, B.P. Anderson, J.M. Bower, Cholinergic modulation of cortical associative memory formation, J. Neurosci. 67 (1992) 1230–1246.

[34] T. Hatfield, J.-S. Han, M. Conley, M. Gallagher, P. Holland, Neurotoxic lesions of basolateral, but not central, amygdala interfere

with Pavlovian second-order conditioning and reinforcer devaluation effects, J. Neurosci. 16 (1996) 5256–5265.

[35] A.M. Himmelheber, M. Sarter, J.P. Bruno, Operant performance and cortical acetylcholine release: role of response rate, reward density, and non-contingent stimuli, Cogn. Brain Res. 6 (1997) 23–36.

[36] A.M. Himmelheber, M. Sarter, J.P. Bruno, Increases in cortical acetylcholine release during sustained attention performance in rats, Cogn. Brain Res. 9 (2000) 313–325.

[37] L.A. Holley, M. Sarter, Functions of cholinergic inputs to visual cortical areas: effects of visual cortical cholinergic deafferentation on visual attention in rats, Soc. Neurosci. Abstr. 21 (1995) 763.4.

[38] L.A. Holley, J. Turchi, C. Apple, M. Sarter, Dissociation between the attentional effects of infusions of a benzodiazepine receptor agonist and an inverse agonist into the basal forebrain, Psychopharmacology 120 (1995) 99–108.

[39] J.B. Hopfinger, M.H. Buonocore, G.R. Mangun, The neural mechanisms of top-down attentional control, Nat. Neurosci. 3 (2000) 284–291.

[40] E. Jodo, C. Chiang, G. Aston-Jones, Potent excitatory influence of prefrontal cortex activity on noradrenergic locus coeruleus neurons, Neuroscience 83 (1998) 63–79.

[41] S. Kastner, L.G. Ungerleider, Mechanisms of visual attention in the human cortex, Annu. Rev. Neurosci. 23 (2000) 315–341.

[42] S. Kastner, P. De Weerd, R. Desimone, L.G. Ungerleider, Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI, Science 282 (1998) 108–111.

[43] F. Kimura, M. Fukuda, T. Tsumoto, Acetylcholine suppresses the spread of excitation in the visual cortex revealed by optical recording: possible differential effect depending on the source of input, Eur. J. Neurosci. 11 (1999) 3597–3609.

[44] R. King, J.V. Corwin, Comparisons of hemi-attention produced by unilateral lesions of the posterior parietal cortex or medial agranular prefrontal cortex in rats: neglect, extinction, and the role of stimulus distance, Behav. Brain Res. 54 (1993) 117–131.

[45] D.E. Kuhl, R.A. Koeppe, S. Minoshima, S.E. Snyder, E.P. Ficaro, N.L. Foster, K.A. Frey, M.R. Kilbourn, In vivo mapping of cerebral acetylcholinesterase activity in aging and Alzheimer's disease, Neurology 52 (1999) 691–699.

[46] R.D. Lane, P.M.L. Chua, R.J. Dolan, Common effects of emotional valence, arousal and attention on neural activation during visual processing of pictures, Neuropsychology 37 (1999) 989–997.

[47] J.C. Lecas, Prefrontal neurons sensitive to increased visual attention in the monkey, NeuroReport 7 (1995) 305–309.

[48] C.M. Mar, D.A. Smith, M. Sarter, Behavioral vigilance in schizophrenia: evidence for hyperattentional processing, Br. J. Psychiatry 169 (1996) 781–789.

[49] A.W. McDonald III, J.D. Cohen, V.A. Stenger, C.S. Carter, Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control, Science 288 (2000) 1835–1838.

[50] J. McGaughy, T. Kaiser, M. Sarter, Behavioral vigilance following infusions of 192 IgG-saporin into the basal forebrain: selectivity of the behavioral impairment and relation to cortical AChE-positive fiber density, Behav. Neurosci. 110 (2) (1996) 247–265.

[51] J. McGaughy, M. Sandstrom, S. Ruland, J.P. Bruno, M. Sarter, Lack of effects of lesions of the dorsal noradrenergic bundle on behavioral vigilance, Behav. Neurosci. 111 (1997) 646–652.

[52] J. McGaughy, M. Sarter, Behavioral vigilance in rats: task validation and the effects of age, amphetamine, and benzodiazepine receptor ligands, Psychopharmacology 117 (1995) 340–357.

[53] J. McGaughy, M. Sarter, Sustained attention performance in rats with intracortical infusions of 192 IgG-saporin-induced cortical cholinergic deafferentation: effects of physostigmine and FG 7142, Behav. Neurosci. 112 (1998) 1519–1525.

[54] T.M. McKenna, J.H. Ashe, G.K. Hui, N.M. Weinberger, Muscarinic agonists modulate spontaneous and evoked unit discharge in auditory cortex of cat, Synapse 2 (1988) 54–68.

[55] M.-M. Mesulam, A cortical network for directed attention and unilateral neglect, Ann. Neurol. 10 (1981) 309–325.

[56] M.-M. Mesulam, Large-scale neurocognitive networks and distributed processing for attention, language, and memory, Ann. Neurol. 28 (1990) 597–613.

[57] L.A.H. Miner, M. Ostrander, M. Sarter, Effects of ibotenic acid-induced loss of neurons in the medial prefrontal cortex of rats on behavioral vigilance: evidence for executive dysfunction, J. Psychopharmacol. 11 (1997) 169–178.

[58] H. Moore, M. Sarter, J.P. Bruno, Bidirectional modulation of cortical acetylcholine efflux by infusion of benzodiazepine receptor ligands into the basal forebrain, Neurosci. Lett. 189 (1995) 31–34.

[59] J.L. Muir, B.J. Everitt, T.W. Robbins, AMPA-induced excitotoxic lesions of the basal forebrain: a significant role for the cortical cholinergic system in attentional function, J. Neurosci. 14 (1994) 2313–2326.

[60] J.L. Muir, B.J. Everitt, T.W. Robbins, The cerebral cortex of the rat and visual attentional function: dissociable effects of mediofrontal, cingulate, anterior dorsolateral, and parietal cortex lesions on a five-choice serial reaction time task, Cereb. Cortex 6 (1996) 470–481.

[61] G.K. Mulholland, D.M. Wieland, M.R. Kilbourn, K.A. Frey, P.S. Sherman, J.E. Carey, D.E. Kuhl, [^{18}F]Fluoroethoxy-benzovesamicol, a PET radiotracer for the vesticular acetylcholine transporter and cholinergic synapses, Synapse 30 (1998) 263–274.

[62] P.C. Murphy, A.M. Sillito, Cholinergic enhancement of direction selectivity in the visual cortex of the cat, Neuroscience 40 (1991) 13–20.

[63] M.J. Nichols, W.T. Newsome, The neurobiology of cognition, Nature 402 (1999) C35–C38.

[64] K. Nobuhara, C. Halldin, H. Hall, P. Karlsson, L. Farde, J. Hiltunen, D.W. McPherson, A. Savonen, K.A. Bergström, S. Pauli, C.G. Swahn, S.A. Larsson, P.O. Schnell, G. Sedvall, Z-IQNP: a potential radioligand for SPECT imaging of muscarinic acetylcholine receptors in Alzheimer's disease, Psychopharmacology 149 (2000) 45–55.

[65] R. Parasuraman, Vigilance, monitoring, and search, in: K. Boff, L. Kaufman, J. Thomas (Eds.), Handbook of Perception and Human Performance, Cognitive Processes and Performance, Vol. 2, Wiley, New York, 1986, pp. 43.1–43.39.

[66] R. Parasuraman, J.V. Haxby, Attention and brain function in Alzheimer's disease: a review, Neuropsychology 7 (1993) 242–272.

[67] R. Parasuraman, J.S. Warm, W.N. Dember, Vigilance: taxonomy and utility, in: L.S. Mark, J.S. Warm, R.L. Huston (Eds.), Ergonomics and Human Factors, Springer Verlag, New York, 1987, pp. 11–39.

[68] J.V. Pardo, T. Fox, M.E. Raichle, Localization of a human system for sustained attention by positron emission tomography, Nature 349 (1991) 61–64.

[69] T. Paus, R.J. Zatorre, N. Hofle, Z. Caramanos, J. Gotman, M. Petrides, A.C. Evans, Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task, J. Cogn. Neurosci. 9 (1997) 392–408.

[70] M.F. Pediconi, A.M. Roccamo de Fernandez, F.J. Barrantes, Asymmetric distribution and down-regulation of the muscarinic acetylcholine receptor in rat cerebral cortex, Neurochem. Res. 18 (1993) 565–572.

[71] R.J. Perry, J.R. Hodges, Attention and executive functions in Alzheimer's disease. A critical review, Brain 122 (1999) 383–404.

[72] C.M. Portas, G. Rees, A.M. Howseman, O. Josephs, R. Turner, C.D. Frith, A specific role for the thalamus in mediating the interaction of attention and arousal in humans, J. Neurosci. 18 (1998) 8979–8989.

[73] M.I. Posner, Interaction of arousal and selection in the posterior attention network, in: A. Baddeley, L. Weiskrantz (Eds.), Attention, Selection, Awareness and Control, Clarendon Press, Oxford, 1993, pp. 390–405.

[74] M.I. Posner, Attention: the mechanisms of consciousness, PNAS 91 (1994) 7398–7403.

[75] M.I. Posner, S.E. Petersen, The attention system of the human brain, Annu. Rev. Neurosci. 13 (1990) 25–42.

[76] M.I. Posner, S.E. Petersen, P.T. Fox, M.E. Raichle, Localization of cognitive operations in the human brain, Science 240 (1988) 1627–1631.

[77] T.W. Robbins, Arousal systems and attentional processes, Biol. Psychol. 45 (1997) 57–71.

[78] T.W. Robbins, Arousal and attention: psychopharmacological and neuropsychological studies in experimental animals, in: R. Parasuraman (Ed.), The Attentive Brain, MIT Press, Cambridge, 1998, pp. 189–220.

[79] T.W. Robbins, B.J. Everitt, H.M. Marston, J. Wilkinson, G.H. Jones, K.J. Page, Comparative effects of ibotenic acid- and quisqualic acid-induced lesions of the substantia innominata on attentional function in the rat: further implications for the role of the cholinergic neurons in the nucleus basalis in cognitive processes, Behav. Brain Res. 5 (1989) 221–240.

[80] A.C. Roberts, J.D. Wallis, Inhibitory control and affective processing in the prefrontal cortex: neuropsychological studies in the common marmoset, Cereb. Cortex 10 (2000) 252–262.

[81] I.H. Robertson, T. Manly, N. Beschin, R. Daini, H. Haeske-Dewick, V. Hömberg, M. Jehkonen, G. Pizzamiglio, A. Shiel, E. Weber, Auditory sustained attention is a marker of unilateral neglect, Neuropsychologia 35 (1997) 1527–1532.

[82] J.B. Rowe, I. Toni, O. Josephs, R.S.J. Frackowiak, R.E. Passingham, The prefrontal cortex: response selection of maintenance within working memory?, Science 288 (2000) 1656–1660.

[83] L. Rueckert, J. Grafman, Sustained attention deficits in patients with right frontal lesions, Neuropsychology 34 (1996) 953–963.

[84] L. Rueckert, J. Grafman, Sustained attention deficits in patients with lesions of posterior cortex, Neuropsychology 36 (1998) 653–660.

[85] M. Sarter, G.G. Berntson, J.T. Cacioppo, Brain imaging and cognitive neuroscience. Toward strong inference in attributing function to structure, Am. Psychol. 51 (1996) 13–21.

[86] M. Sarter, J.P. Bruno, Cognitive functions of cortical ACh (acetylcholine): lessons from studies on the trans-synaptic modulation of activated efflux, Trends Neurosci. 17 (1994) 217–221.

[87] M. Sarter, J.P. Bruno, Cognitive functions of cortical acetylcholine: toward a unifying hypothesis, Brain Res. Rev. 23 (1997) 28–46.

[88] M. Sarter, J.P. Bruno, Abnormal regulation of corticopetal cholinergic neurons and impaired information processing in neuropsychiatric disorders, Trends Neurosci. 22 (1999) 67–74.

[89] M. Sarter, J.P. Bruno, Cortical cholinergic inputs mediating arousal, attentional processing, and dreaming: differential afferent regulation of the basal forebrain by telencephalic and brainstem afferents, Neuroscience 95 (2000) 933–952.

[90] H. Sato, Y. Hata, K. Hagihara, T. Tsumoto, Effects of cholinergic depletion on neuron activities in the cat visual cortex, J. Neurophysiol. 58 (1987) 781–794.

[91] W. Schultz, A. Dickinson, Neuronal coding of prediction errors, Annu. Rev. Neurosci. 23 (2000) 473–500.

[92] T. Shallice, P.W. Burgess, Deficits in strategy application following frontal lobe damage in man, Brain 114 (1991) 727–741.

[93] G.L. Shulman, M. Corbetta, R.L. Buckner, M.E. Raichle, J.A. Fiez, F.M. Miezin, S.E. Peterson, Top-down modulation of early sensory cortex, Cereb. Cortex 7 (1997) 193–206.

[94] J.R. Stowell, G.G. Berntson, M. Sarter, Attenuation of the bidirectional effects of chlordiazepoxide and FG 7142 on conditioned response suppression and associated cardiovascular reactivity by loss of cortical cholinergic inputs, Psychopharmacology 150 (2000) 141–149.

[95] D.T. Stuss, T. Shallice, M.P. Alexander, T.W. Picton, A multidisciplinary approach to anterior attentional functions, Ann. NY Acad. Sci. 769 (1995) 191–211.

[96] J.A. Swets, R.M. Pickett, Evaluation of Diagnostic Systems. Methods From Signal Detection Theory, Academic Press, New York, 1982.

[97] A.M. Treisman, G. Gelade, A feature-integration theory of attention, Cogn. Psychol. 12 (1980) 97–136.

[98] N. Tremblay, R.A. Warren, R.W. Dykes, Electrophysiological studies of acetylcholine and the role of the basal forebrain in the somatosensory cortex of the cat. II. Cortical neurons excited by somatic stimuli, J. Neurophysiol. 64 (1990) 1212–1222.

[99] J. Turchi, M. Sarter, Cortical acetylcholine and processing capacity: effects of cortical cholinergic deafferentation on crossmodal divided attention in rats, Cogn. Brain Res. 6 (1997) 147–158.

[100] J. Turchi, M. Sarter, Bidirectional modulation of basal forebrain NMDA receptor function differentially affects visual attentional abut not visual discrimination performance, Neuroscience, in press.

[101] J. Turchi, M. Sarter, Cortical cholinergic inputs mediate processing capacity: effects of 192 IgG-saporin-induced lesions on olfactory span performance, Eur. J. Neurosci. 12 (2000) 4505–4514.

[102] M.L. Voytko, D.S. Olton, R.T. Richardson, L.K. Gorman, J.R. Tobin, D.L. Price, Basal forebrain lesions in monkeys disrupt attention but not learning and memory, J. Neurosci. 14 (1994) 167–186.

[103] N.M. Weinberger, Learning-induced changes in auditory receptive fields, Curr. Opin. Neurobiol. 3 (1993) 570–577.

[104] N.M. Weinberger, Dynamic regulation of receptive fields and maps in the adult sensory cortex, Annu. Rev. Neurosci. 18 (1995) 129–158.

[105] I.M. White, S.P. Wise, Rule-dependent neuronal activity in the prefrontal cortex, Exp. Brain Res. 126 (1999) 315–335.

[106] Z. Xiang, J.R. Huguenard, D.A. Price, Cholinergic switching within neocortical inhibitory networks, Science 281 (1998) 985–988.

[107] L. Zaborszky, R.P. Gaykema, D.J. Swanson, W.E. Cullinans, Cortical input to the basal forebrain, Neuroscience 79 (1997) 1051–1078.