

# Nicotinic acetylcholine receptors in attention circuitry: the role of layer VI neurons of prefrontal cortex

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**Abstract** Cholinergic modulation of prefrontal cortex is essential for attention. In essence, it focuses the mind on relevant, transient stimuli in support of goal-directed behavior. The excitation of prefrontal layer VI neurons through nicotinic acetylcholine receptors optimizes local and top-down control of attention. Layer VI of prefrontal cortex is the origin of a dense feedback projection to the thalamus and is one of only a handful of brain regions that express the  $\alpha 5$  nicotinic receptor subunit, encoded by the gene *chrna5*. This accessory nicotinic receptor subunit alters the properties of high-affinity nicotinic receptors in layer VI pyramidal neurons in both development and adulthood. Studies investigating the consequences of genetic deletion of  $\alpha 5$ , as well as other disruptions to nicotinic receptors, find attention deficits together with altered cholinergic excitation of layer VI neurons and aberrant neuronal morphology. Nicotinic receptors in prefrontal layer VI neurons play an essential role in focusing attention under challenging circumstances. In this regard, they do not

act in isolation, but rather in concert with cholinergic receptors in other parts of prefrontal circuitry. This review urges an intensification of focus on the cellular mechanisms and plasticity of prefrontal attention circuitry. Disruptions in attention are one of the greatest contributing factors to disease burden in psychiatric and neurological disorders, and enhancing attention may require different approaches in the normal and disordered prefrontal cortex.

**Keywords** Nicotinic acetylcholine receptors · Attention · *chrna5* · Medial prefrontal cortex · Electrophysiology

Attention has been eloquently described as the ‘search-light’ that focuses on relevant information in the midst of distraction in order to support goal-directed behavior [1]. In particular, it plays a pivotal role in mediating the executive functions of the prefrontal cortex [2, 3], a site of sensorimotor and emotional integration that is uniquely positioned to execute top-down control permissive to the orchestration of complex, flexible, and purposeful behavior such as problem solving, planning, and decision making [1, 3–5]. Given its intimate relationship to awareness, attention has also been qualified as the gateway to consciousness [2, 3, 6, 7].

Acetylcholine has long been known to play a role in cognition [8–10]. Non-specific lesions of the cholinergic neurons of the basal forebrain first suggested a more specific involvement of acetylcholine in attention [11–16], and it subsequently became clear that cholinergic projections to the prefrontal cortex are especially important in this regard [17, 18]. The importance of cholinergic modulation of prefrontal cortex can be seen in the detrimental effects for attention of specific lesions to its cholinergic projections. These projections, as shown in the schematic in Fig. 1,

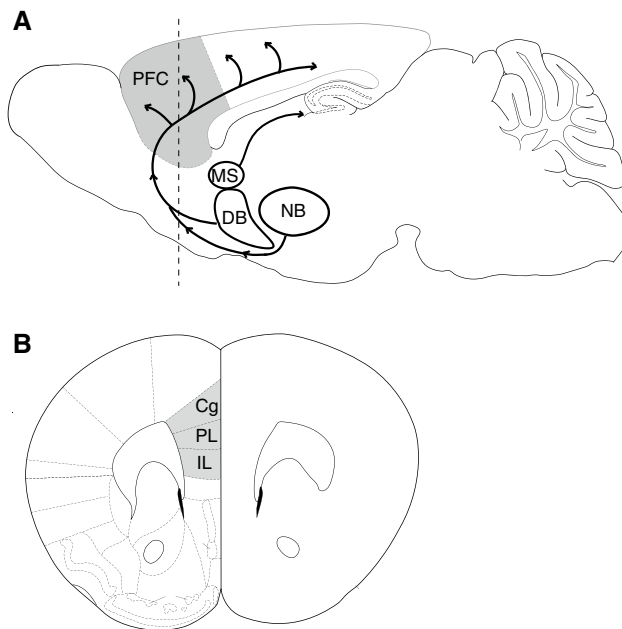
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**Fig. 1** **a** The medial prefrontal cortex shown in gray receives cholinergic innervation from the basal forebrain. Figure adapted from Woolf [25] and Paxinos and Franklin [277] and is based on findings from Rye et al., Luiten et al., and Gaykema et al. [23, 160, 278]. The *dashed line* indicates the approximate location of the coronal section shown below. **b** Coronal brain section showing the subregions of rodent medial prefrontal cortex (in *gray*). *Cg* cingulate cortex, *DB* diagonal band, *IL* infralimbic cortex, *MS* medial septal nucleus, *NB* nucleus basalis, *PFC* prefrontal cortex, *PL* prelimbic cortex

include a dense cholinergic innervation from the basal forebrain, principally from the basal nucleus and parts of the diagonal band, but also from the magnocellular preoptic nucleus and substantia innominata [19–26]. Intrabasalis infusions of the cholinergic immunotoxin 192 IgG-saporin lead to the loss of cortical cholinergic afferents, reduced acetylcholine efflux in the prefrontal cortex, and significant impairments on attention tasks [27, 28]. Bilateral infusions of 192 IgG saporin in medial prefrontal cortex are equally detrimental and demonstrate that its deafferentation of cholinergic projections is sufficient to produce attentional impairments [17, 18, 29].

The importance of prefrontal cholinergic modulation was further suggested by microdialysis studies showing robust acetylcholine efflux within the prefrontal cortex during the performance of attention tasks [30–32], which reflects both attentional effort [33, 34] and behavioral context [35]. Moreover, the development of choline-sensitive microelectrodes, which offer greater temporal resolution than microdialysis probes, has further revealed that acetylcholine release in the prefrontal cortex increases rapidly and transiently—on the timescale of seconds to minutes—during the performance of attention tasks [29] where, as we will emphasize in this review, it can exert profound effects

on corticothalamic neurons via the nicotinic acetylcholine receptors [36–38].

### Layer VI corticothalamic neurons of the prefrontal cortex play a central role in attention

Acetylcholine optimizes prefrontal cortical circuitry for top-down control [39–41]. Corticothalamic neurons, which constitute a large proportion of layer VI pyramidal cells [42], are uniquely positioned to exert these top-down influences and are robustly excited by acetylcholine [36]. These neurons integrate highly processed information from layer V pyramidal cells, from layer VI cortico-cortical neurons, and from direct thalamic inputs [42]. In turn, they exert powerful feedback influences on the thalamus [43–46]. While not all neurons in layer VI are corticothalamic, it is important to note that there are ten times more corticothalamic feedback projections than there are thalamocortical afferents [47], such that cholinergic modulation of these neurons will exert important influences on the circuits of attention.

Layer VI corticothalamic neurons constitute the major source of excitatory afferents to the thalamus [48], where they affect both the inhibitory reticular thalamic neurons [49] and the excitatory thalamocortical projection neurons [50]. During the tonic firing of wakefulness, the overall effect of this corticothalamic feedback is to *focus* thalamic and thalamocortical excitation [51], in part by modulating the sensitivity of thalamic neurons to incoming sensory stimuli [48, 52–54]. Prefronto-thalamic connectivity is further privileged in its modulation of attention due to its relationship with the midline and intralaminar thalamic nuclei that have long been implicated in awareness and attention [54–58].

The high percentage of layer VI neurons responding to acetylcholine [59] suggests that corticothalamic neurons are not the exclusive population of neurons subject to cholinergic modulation. This point should be emphasized since recent work has shown that layer VI neurons as a class exert powerful gain control over all the other cortical layers [60]. Cholinergic innervation is present in all layers of the prefrontal cortex [24, 26], but appears biased toward activation of the deepest layers [61]. Clear labeling of cholinergic fibers is observed in the deep cortical layers [24, 26], as demonstrated with immunostaining for choline-acetyltransferase (ChAT), the enzyme that catalyzes the synthesis of acetylcholine from acetyl-CoA and choline. Furthermore, anterograde labeling of ChAT positive cholinergic afferents from the basal forebrain indicate preferential projection to deep layers V/VI [62]. The apical dendrites from a large fraction of layer VI neurons extend all the way to the pial surface [63], where they may also

be stimulated by cholinergic projections (and possibly also by cholinergic interneurons [64]) in superficial layers II/III [26, 64].

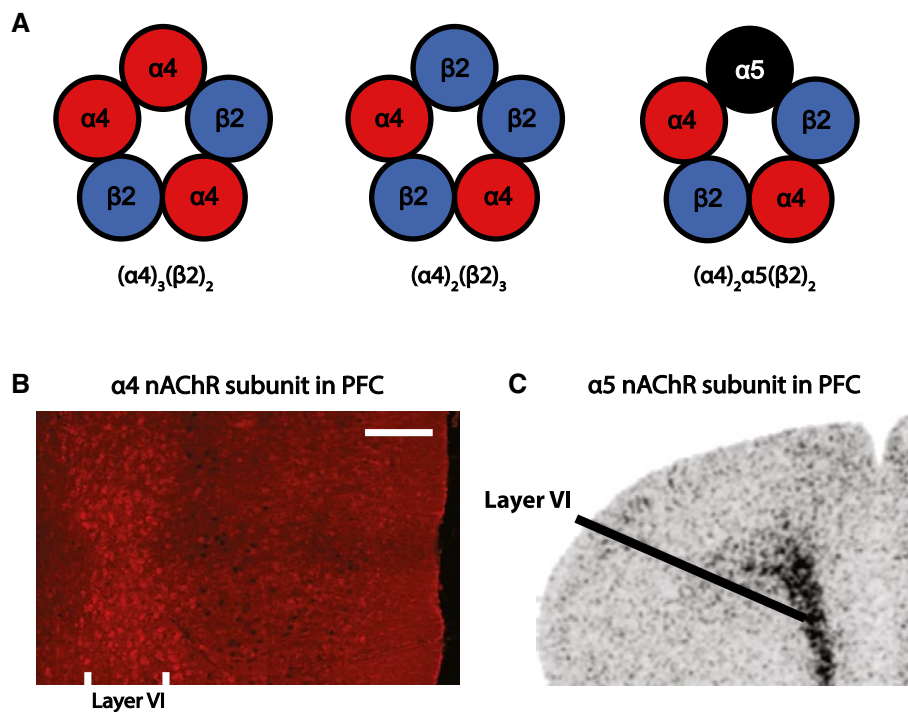
### Nicotinic acetylcholine receptors and their modulation of prefrontal layer VI neurons

The neurotransmitter acetylcholine acts on two classes of receptors—the ionotropic nicotinic receptors, which are the main focus of this review, and the metabotropic muscarinic acetylcholine receptors, which are G-protein coupled. Nicotinic acetylcholine receptors are pentameric ligand-gated cation channels [65, 66], permeable to  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{2+}$  ions [65, 67]. Two families of subunits can contribute to the pentameric structure necessary for functional nicotinic receptors: the  $\alpha$  subunits ( $\alpha 2$ – $\alpha 10$ ) and the  $\beta$  subunits ( $\beta 2$ – $\beta 4$ ) [65, 66, 68]. They are arranged in a pinwheel around a central pore, assembled either as  $\alpha$ -containing homomers or  $\alpha/\beta$  heteromers. Nicotinic receptors are widely expressed in the central nervous system, and subunit composition differs from one region to the next [65, 66]. The subunit composition and stoichiometry of nicotinic receptors influence

their functional properties, with important implications for nicotinic signaling [37, 69–72].

The most widely expressed nicotinic acetylcholine receptors in the brain are the  $\alpha 4\beta 2$ -containing receptors ( $\alpha 4\beta 2^*$ ) [65, 73–75], which are prominently expressed throughout cortex [76–79]. The homomeric  $\alpha 7$  nicotinic receptors are also expressed in cortex, although only weak labeling has been documented in cortical layer VI [80]. Interestingly, while the  $\alpha 4$ ,  $\alpha 5$ ,  $\alpha 7$ , and  $\beta 2$  nicotinic receptor subunits show similar expression patterns in rodent and primate brain [81], there are some species differences in the expression of nicotinic receptors with potential implications for cholinergic modulation of attention circuitry. For example, the  $\alpha 2$  nicotinic subunit is only widely expressed in primate brain [81], although it is not enriched in layer VI.

The  $\alpha 4\beta 2^*$  receptors have high affinity for nicotinic agonists (including acetylcholine and nicotine) and desensitize slowly, on the timescale of seconds [65, 82–84]. As illustrated in the schematic in Fig. 2, the  $\alpha 4\beta 2^*$  nicotinic receptors can assume different stoichiometries, including  $(\alpha 4)_2(\beta 2)_3$  and  $(\alpha 4)_3(\beta 2)_2$ . In the relatively rare brain regions that express the accessory  $\alpha 5$  nicotinic subunit,



**Fig. 2** Subunit composition and layout of nicotinic acetylcholine receptor subunits in layer VI of medial prefrontal cortex. **a** Schematics showing three possible compositions of  $\alpha 4\beta 2^*$  nicotinic receptors within layer VI neurons of medial prefrontal cortex. Figure adapted from McKay et al. [279]. **b** Photomicrograph of mouse medial prefrontal cortex immunostained for YFP-tagged nicotinic acetylcholine

receptor  $\alpha 4$  subunits, putatively expressed in  $\alpha 4\beta 2^*$ -containing cells as shown at lower resolution by Marks and colleagues [93]. White matter on the right and the medial pial surface is on the left; adapted from Alves et al. [92]. Scale bar 200  $\mu\text{m}$ . **c** In situ hybridization showing a dense band of  $\alpha 5$  nicotinic subunit mRNA expression in layer VI of the medial prefrontal cortex; adapted from Wada et al. [86]

such as layer VI of prefrontal cortex [86], these receptors can also incorporate the accessory  $\alpha 5$  subunit to form  $(\alpha 4)_2(\beta 2)_2(\alpha 5)$  receptors ( $\alpha 4\alpha 5\beta 2$ ) [65, 66, 85–88]. The accessory  $\alpha 5$  subunits cannot form functional channels by themselves, since they do not contribute to the acetylcholine binding site and thus require co-assembly with other  $\alpha$  and  $\beta$  subunits [65, 79]. However, inclusion of  $\alpha 5$  can alter  $\alpha 4\beta 2^*$  nicotinic receptor properties substantially [71, 87, 88]: it can enhance receptor assembly and expression [87, 89], modulate receptor sensitivity to acetylcholine [37, 65, 69, 88, 90, 91], increase  $\text{Ca}^{2+}$  permeability [88], and confer sensitivity to allosteric modulation by galanthamine [36, 88].

Immunohistochemistry for YFP-tagged nicotinic  $\alpha 4$  subunits in a knockin mouse suggests that high-affinity nicotinic receptors are densely expressed in layer VI of prefrontal cortex [92], where the accessory  $\alpha 5$  subunit is also prominently expressed [86, 93–95]. Interestingly, while only one-fifth of all  $\alpha 4\beta 2^*$  nicotinic receptors in the brain are estimated to contain the  $\alpha 5$  accessory subunit [65, 89, 96], prefrontal layer VI nicotinic receptors appear to incorporate  $\alpha 5$  to a disproportionately large extent [37]. Indeed, functional concentration–response analyses of prefrontal corticothalamic neurons from WT and  $\alpha 5$  knockout mice ( $\alpha 5^{-/-}$ ) suggest that the vast majority of  $\alpha 4\beta 2^*$  nicotinic receptors of its layer VI neurons are affected by this subunit [37]. As we will see, this unique expression pattern has ramifications for attentional signaling and behavior [37].

During the performance of attention tasks, brief transients of acetylcholine are released in medial prefrontal cortex [97, 98]. Population calcium imaging in slices of prefrontal cortex has demonstrated that nicotinic receptor stimulation by acetylcholine predominantly activates neurons within the deep cortical layers V/VI [61]. At the cellular level, acetylcholine elicits robust excitatory responses in the layer VI corticothalamic neurons of the medial prefrontal cortex that appear to be directly mediated by stimulation of somatodendritic postsynaptic  $\alpha 4\alpha 5\beta 2$  nicotinic receptors [36, 37, 59]. Acetylcholine binding to the nicotinic receptor leads to rapid conformational changes that result in channel opening and the flow of  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{2+}$  cations through the pore [65, 66, 83]. Nicotinic receptors rectify at more depolarized membrane potential [99, 100], such that acetylcholine likely exerts more profound effects near the resting membrane potential, where the effect of nicotinic stimulation is excitatory and results in depolarization. When sufficiently large, this membrane depolarization can lead to the generation of action potentials. Acetylcholine depolarizes the vast majority of layer VI pyramidal cells in this way [36], but these excitatory nicotinic responses are completely eliminated in  $\beta 2^{-/-}$  mice [38, 59], which lack functional  $\alpha 4\beta 2^*$  nicotinic receptors, and are significantly reduced in  $\alpha 5^{-/-}$  mice [59].

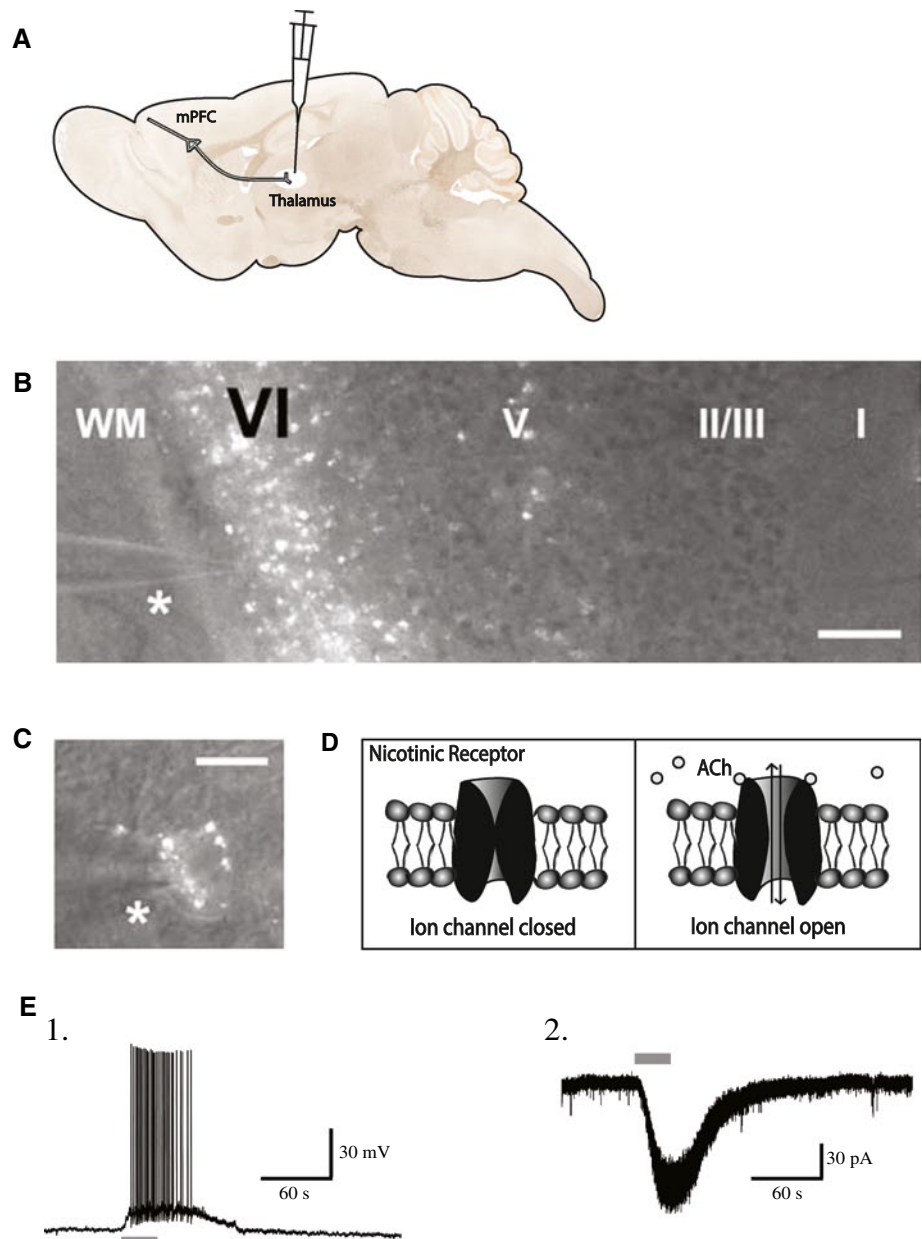
The nicotinic responses that result from the current carried by the flow of  $\text{Na}^+$ ,  $\text{K}^+$ , and  $\text{Ca}^{2+}$  ions through the nicotinic receptor pore can be examined electrophysiologically in voltage clamp (where the membrane potential can be held constant experimentally so as to allow the measurement of the nicotinic current) or in current clamp (where the membrane potential is allowed to fluctuate and the injected current, or lack thereof, is held constant). Figure 3 illustrates the robust excitatory effects of nicotinic stimulation that were recorded in retrogradely labeled corticothalamic neurons in slices of prefrontal cortex [36]. Since corticothalamic neurons can also be distinguished from cortico-cortical cells based on electrophysiological properties [101, 102], Kassam et al. [36] were further able to establish that nicotinic stimulation exerts more profound excitation of cortico-thalamic than cortico-cortical neurons of layer VI prefrontal cortex.

The excitatory nicotinic responses of layer VI pyramidal neurons are directly mediated by postsynaptic somatodendritic receptors since currents are resistant to blockade of synaptic transmission by the  $\text{Na}^+$  channel antagonist tetrodotoxin and to pharmacological inhibition of ionotropic and metabotropic glutamate receptors [36]. Pharmacologically, these nicotinic currents are suppressed by the  $\alpha 4\beta 2^*$  competitive antagonist DH $\beta$ E, insensitive to the  $\alpha 7$  antagonist MLA and potentiated by the  $\alpha 5$  allosteric modulator galanthamine [36, 88]. These findings are consistent with  $\alpha 4\alpha 5\beta 2$  nicotinic receptor involvement [36]. Most convincing, however, is the demonstration that nicotinic excitation of layer VI pyramidal cells is substantially reduced in mice in which the  $\alpha 5$  subunit has been genetically deleted ( $\alpha 5^{-/-}$ ) [37]. Together, these findings highlight that the relatively rare  $\alpha 5$  subunit plays an important role in mediating optimal cholinergic excitation of layer VI neurons of the prefrontal cortex, where it is densely expressed and incorporated into  $\alpha 4\beta 2^*$  nicotinic receptors.

### Nicotinic receptors and attentional performance

At the behavioral level, the  $\alpha 5$  subunit is required for normal attention performance under challenging conditions [37]. The five-choice serial reaction time task (5-CSRTT) is a commonly used attention task that involves sustained and divided attention [103]. Briefly, the animal is placed in an operant chamber, illustrated in Fig. 4. A light stimulus, whose duration can be varied to alter the difficulty of the attention task, is randomly flashed in one of five apertures. The animal is required to attend to, and subsequently accurately recall, the location of this stimulus within a fixed time period. Attention performance is assessed by correct identification of the location of the stimulus by nose poke. This task measures various aspects of attentional control,

**Fig. 3** Acetylcholine (ACh) excites labeled corticothalamic neurons in layer VI of medial prefrontal cortex. **a** Retrograde labeling of corticothalamic neurons through in vivo stereotaxic surgery to inject rhodamine microspheres into the medial dorsal thalamus. **b** Prominent retrograde labeling of layer VI neurons in a coronal prefrontal brain slice. The *asterisk* marks the location of a patch pipette for electrophysiological recordings. *Scale bar* 240  $\mu\text{m}$ . Figure adapted from Kassam et al. [36]. **c** A high-magnification view of a labeled pyramidal cell body. *Scale bar* 20  $\mu\text{m}$ . Figure adapted from Kassam et al. [36]. **d** Schematic showing the closed and open states of the nicotinic acetylcholine receptor. **e** A retrograde-labeled corticothalamic neuron in layer VI of medial prefrontal cortex responds to acetylcholine in (1) current clamp and (2) voltage clamp. Figure adapted from Kassam et al. [36]



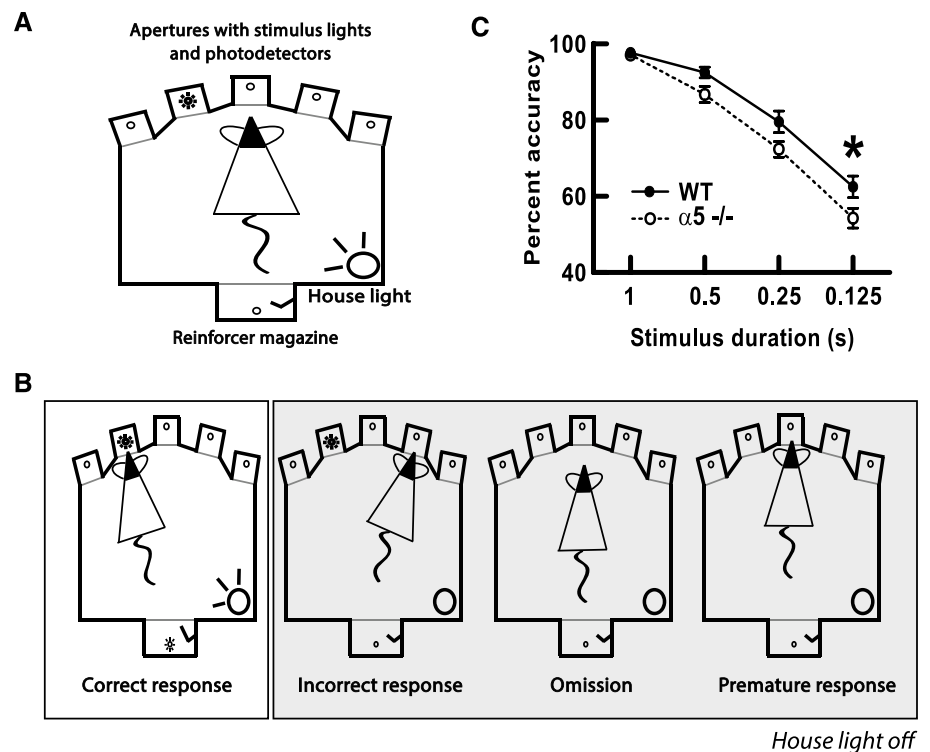
including accuracy (correct responses), omissions (lack of response, reflects inattentiveness), perseveration (repeated responses at the same location, reflects lack of flexibility), and premature responses (responding before the end of the inter-trial interval, reflects impulsivity). The  $\alpha 5^{-/-}$  mice show deficits in accuracy on the 5-CSRTT when stimulus duration is brief, a condition that requires greater attentional demand, but perform normally under baseline training conditions, when stimulus duration is longer. Interestingly, equivalent deficits in attention performance in humans are highly disruptive to cognitive function [104–107]. Mice lacking the  $\beta 2$  subunit ( $\beta 2^{-/-}$ ) also show significant impairments on the 5-CSRTT, and these deficits

can be rescued by lentiviral vector-mediated re-expression of  $\beta 2$ -containing nicotinic receptors in the prefrontal cortex [38]. The 5-CSRTT studies in  $\alpha 5^{-/-}$  and  $\beta 2^{-/-}$  mice employed different training and testing approaches, which may explain subtle differences in the nature of the attention deficit observed [37, 38].

#### Compensatory plasticity of cholinergic responses in prefrontal layer VI neurons

The question arises whether the differences in attention performance observed in  $\alpha 5^{-/-}$  mice result completely

**Fig. 4** Under challenging conditions, mice lacking the nicotinic  $\alpha 5$  subunit ( $\alpha 5^{-/-}$ ) respond with decreased accuracy relative to wild-type (WT) mice in the 5-choice serial reaction time task (5-CSRTT). **a** Schematic of the operant chamber for the 5-CSRTT. **b** Four typical responses of mice performing the 5-CSRTT. From left to right: the correct response, the incorrect response, an omission, and a premature response. Figure adapted from Dalley et al. [280]. **c** Nicotinic receptor  $\alpha 5^{-/-}$  mice perform significantly worse than wild-type controls in the 5-CSRTT when stimulus duration is brief. Figure adapted from Bailey et al. [37]



from the impaired nicotinic stimulation of  $\alpha 4\alpha 5\beta 2$ -containing nicotinic receptors within corticothalamic circuits of adult prefrontal cortex or whether the loss of this nicotinic stimulation leads to functional or structural alterations of attention circuitry. It is conceivable that plasticity in the cholinergic system might ameliorate attention deficits that might otherwise be more severe; for example, allowing  $\alpha 5^{-/-}$  mice to perform at near-normal levels of accuracy when longer stimulus durations are used in the 5-CSRTT [37].

We have observed that cholinergic excitation of the layer VI pyramidal cells primarily involves nicotinic receptors in wild-type mice [59]; however, genetic deletion of the nicotinic  $\alpha 5$  or  $\beta 2$  subunits ( $\alpha 5^{-/-}$  and  $\beta 2^{-/-}$ , respectively) leads to the compensatory upregulation of muscarinic acetylcholine receptor excitation [59]. These G-protein coupled receptors couple to second messenger cascades and exert slower excitatory actions, significantly changing the mechanisms and timing of the cholinergic response in these layer VI neurons [59]. A schematic of this compensatory plasticity is shown in Fig. 5; it appears to affect neurons from  $\beta 2^{-/-}$  mice to a greater degree than those from  $\alpha 5^{-/-}$  mice [59]. This unusual plasticity of layer VI cholinergic responsiveness indicates that the attention impairments associated with disruption of nicotinic signaling are more complex than originally anticipated. It is unclear at what stage of maturation this plasticity occurs and whether it can be reversed given sufficient time after adult rescue of the missing nicotinic receptor subunits [38].

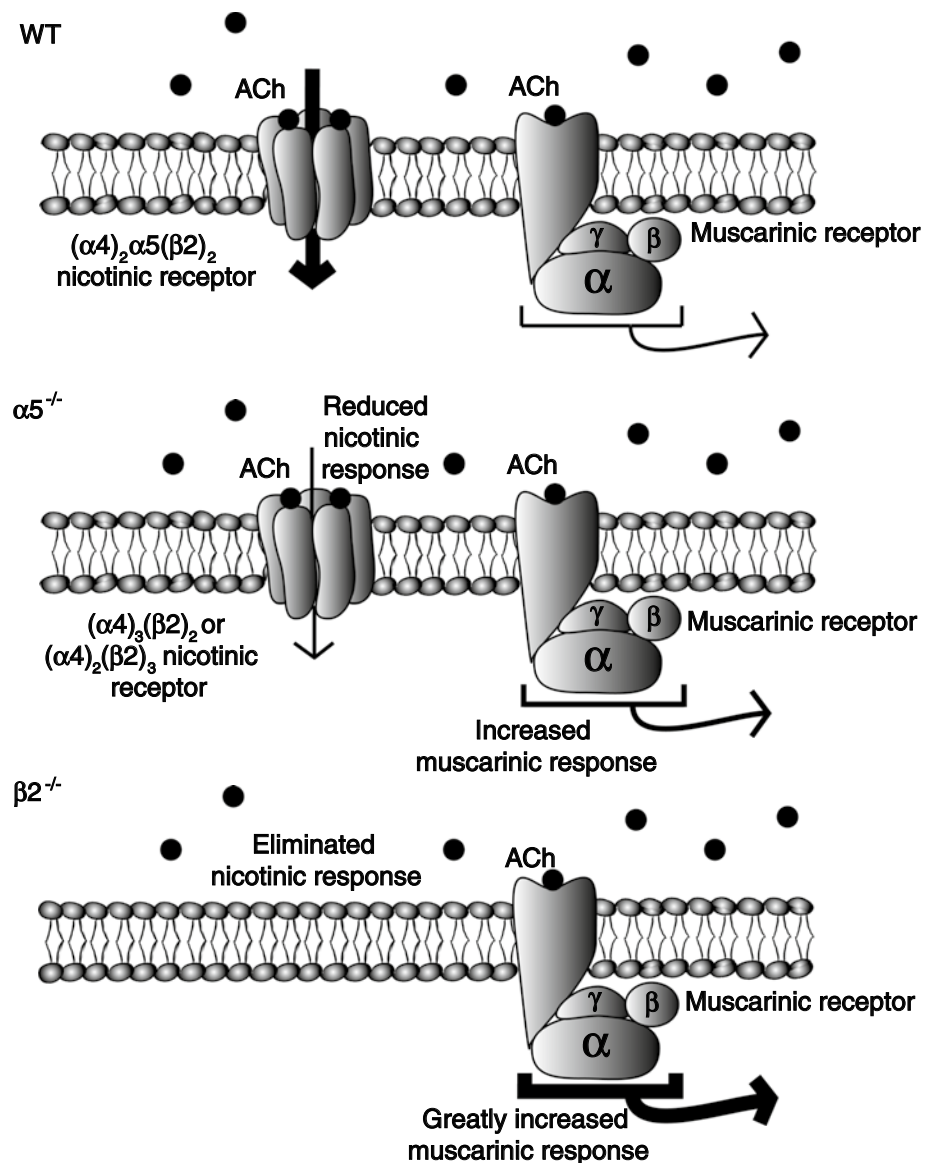
#### Nicotinic receptor $\alpha 5$ subunit and morphological maturation of prefrontal layer VI neurons

The maturation of executive function and attention requires the normal development of prefrontal cortex [108–110], and developmental lesions of the cholinergic system disrupt neuronal morphology and cortical circuitry [111–114]. Cortical nicotinic acetylcholine receptors play an important role in the development of attention circuitry [36, 63, 115], and aberrations in cortical nicotinic binding are reported to occur in many neurodevelopmental disorders, including autism [116, 117], epilepsy [118], and schizophrenia [119, 120].

Cholinergic innervation of the prefrontal cortex is well developed by the third week of postnatal life in rodents [121, 122], a time period equivalent to the perinatal period in humans [123, 124]. Dense ChAT immunostaining can be seen in the frontal cortex at this time [122], and high levels of  $\alpha 4\beta 2^*$  nicotinic binding are observed in prefrontal layer VI [125]. Furthermore, peak mRNA levels for the  $\alpha 5$  subunit are seen in layer VI during the first 2–3 weeks of postnatal development [95]. By contrast, cortical mRNA levels for the  $\alpha 4$  and  $\beta 2$  subunits show a somewhat different pattern with a peak at birth and a slight decline before maintaining relatively constant expression across postnatal development [126, 127].

Developmental differences in nicotinic excitation and dendritic morphology coincide temporally with changes in  $\alpha 5$  expression. The excitatory nicotinic currents of layer VI

**Fig. 5** Plasticity between nicotinic and muscarinic acetylcholine (ACh) receptors in layer VI neurons of medial prefrontal cortex. Typical responses in layer VI pyramidal neurons are highly driven by nicotinic receptors, whereas muscarinic effects are less prominent. In knockout mice with decreased nicotinic receptor function, muscarinic responses are enhanced. This compensatory upregulation in muscarinic receptor function is apparent in  $\alpha 5^{-/-}$  mice and very pronounced in  $\beta 2^{-/-}$  mice. Figure summarizing results from Tian et al. [59]



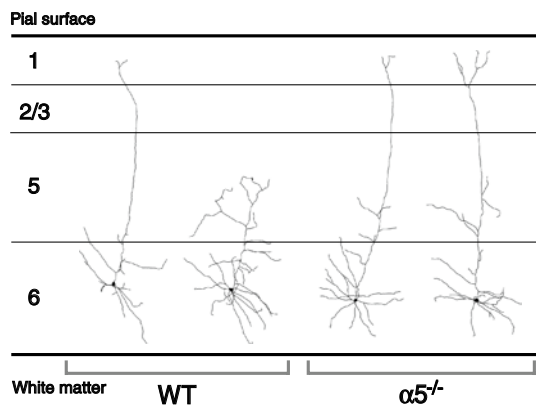
neurons exhibit a developmental profile, peaking within the first postnatal month [36]. Nicotinic stimulation can influence neuronal morphology and spur neurite retraction [128, 129], and in the first morphological analysis of these cells, Bailey et al. [63] showed that key developmental changes in neuronal complexity appear to be initiated within this critical time period. Specifically, there appears to be a developmental retraction of the apical dendrites of layer VI prefrontal cortex: whereas almost all the apical dendrites of layer VI pyramidal neurons extend to the pial surface in young mice at postnatal week 3, half of them terminate in the mid-layers by adulthood [63]. As illustrated in Fig. 6, these maturational changes in the dendritic morphology of layer VI neurons are absent in the  $\alpha 5^{-/-}$  mice, without any further differences in overall cortical morphology [63]. Furthermore, layer VI neurons of  $\alpha 5^{-/-}$  mice show negligible

developmental changes in nicotinic excitation [63]. Thus, the  $\alpha 5$  subunit appears to be essential for the normal maturation of corticothalamic circuitry and drives developmental differences in layer VI excitation and morphology.

In summary, there are extensive differences between WT and  $\alpha 5^{-/-}$  mice in development and adulthood. These differences are relevant to the deficits in attention performance seen in  $\alpha 5^{-/-}$  mice in adulthood and are summarized in Table 1.

### Sex differences in nicotinic excitation of layer VI neurons during postnatal development

Interestingly, there are also developmental sex differences in nicotinic excitation [92]. Prefrontal layer VI nicotinic



**Fig. 6** The morphology of layer VI neurons in medial prefrontal cortex differs between wild-type and  $\alpha 5^{-/-}$  mice. In adult wild-type mice, there is a roughly equal distribution of layer VI pyramidal neurons that have long apical dendrites that terminate at the pial surface and those that have short apical dendrites that terminate within the mid-layers of the medial prefrontal cortex. In contrast, layer VI neurons of  $\alpha 5^{-/-}$  mice show a preponderance of neurons with long apical dendrites. In this sense, it could be said the layer VI neurons of  $\alpha 5^{-/-}$  mice retain a developmental phenotype in the pattern of their apical dendritic morphology. In young mice of both genotypes, layer VI neurons have only long apical dendrites. Figure adapted from Bailey et al. [63]. Of note, these morphological changes can be recapitulated in wild-type mice by chronic in vivo nicotine treatment during development [281], likely mediated through desensitization of nicotinic receptors [281]

currents show a similar developmental profile in males and females, with peak nicotinic excitation achieved around the 3rd week of postnatal life and declining by the 5th week. However, within the 1st postnatal month, nicotinic currents

are larger and observed in a greater proportion of cells in males than in females. It is not known whether there are any sex differences in  $\alpha 5$  expression or function, although it appears that a similar percentage of layer VI neurons express  $\alpha 4$  nAChRs in developing male and female mice [92]. In fact, this sex difference in nicotinic excitation of layer VI neurons during postnatal development may arise from differences in cortical neurosteroid levels between males and females. The sex steroid progesterone, for example, can directly suppress nicotinic currents through negative allosteric modulation of  $\alpha 4\beta 2^*$  nAChRs [130, 131]. The pre-pubertal rodent brain expresses all the enzymes necessary for the de novo synthesis of progesterone from cholesterol [132, 133], and the rate-limiting enzyme in this pathway shows a trend toward greater cortical expression in females than males at this stage of development [132]. Furthermore, evidence suggests that estrogenic steroid hormones may directly interact with the nicotinic receptor to potentiate excitatory ACh responses [134]. Developmental sex differences in the maturation of attention circuitry may help account for vulnerability to attention deficit disorders, which are twice as prevalent in males than females [135–137].

#### Additional mechanisms of cholinergic modulation of prefrontal cortex

Although nicotinic receptors located on pyramidal neurons in layer VI of the medial prefrontal cortex play a critical role in mediating attentional processes, they do not act in

**Table 1** Categories of differences between WT and  $\alpha 5^{-/-}$  mice

Effects	WT	$\alpha 5^{-/-}$
Neuropharmacology in layer VI pyramidal cells [37, 59, 63]		
ACh-elicited nicotinic receptor currents (1 mM)	40 ± 5 pA	14 ± 1 pA*
Nicotine-elicited nicotinic receptor currents (300 nM)	16 ± 2 pA	6 ± 1 pA*
Desensitization (% decrease) of ACh response after nicotine	36 ± 4 %	73 ± 4 %*
ACh-elicited muscarinic depolarization from rest	2.9 ± 0.5 mV	6.5 ± 1.3 mV*
ACh-elicited muscarinic increase in spiking frequency in excited state	309 ± 23 %	462 ± 65 %*
Developmental changes in ACh-induced currents	Peak in young mice	No change*
Dendritic morphology of layer VI pyramidal cells [63]		
Young mice: % apical dendrites extending to the pial surface	82 %	92 %
Adult mice: % apical dendrites extending to the pial surface	45 %	92 %*
Attention behavior [37]		
Performance accuracy on non-demanding attention tasks	98 ± 1 %	97 ± 1 %
Performance accuracy on demanding attention tasks	63 ± 3 %	54 ± 3 %*
Systemic nicotine changes attentional accuracy on demanding tasks	-5 ± 1 %**	-1 ± 4 %

Data are shown as mean ± SEM (where appropriate)

\* Indicates a statistically significant difference from WT with  $P < 0.05$

\*\* Indicates a statistically significant change from baseline with  $P < 0.05$



isolation. There are cholinergic receptors on other prefrontal neurons and on neurons in other brain regions that also contribute to attentional processing in prefrontal cortex. Relevant cholinergic receptors within prefrontal cortex itself include those on layer V neurons, on the terminals of thalamocortical projections, monoaminergic projections, and on cortical interneurons.

Acetylcholine exerts layer-specific effects in the prefrontal cortex [61], and although nicotinic stimulation exerts many effects across the prefrontal cortical column, it appears to enhance preferentially deep layer activation [61]. An elegant optogenetic study by Olsen et al. [60] has recently demonstrated that in the visual cortex, activation of layer VI cells exerts powerful gain control by means of feedback inhibition of the cortical column. It is tempting to speculate that preferential activation of the deep layers of prefrontal cortex by acetylcholine facilitates such information processing. As we have seen, layer VI pyramidal neurons show a robust excitatory response to acetylcholine mediated by postsynaptic somatodendritic nicotinic receptors [36, 37]. In contrast to layer VI, the layer V pyramidal neurons of the prefrontal cortex are predominantly subject to muscarinic modulation [138], although a rapid  $\alpha 7$ -mediated nicotinic response has been documented in the prefrontal cortex of juvenile mice [61]. Importantly in this layer,  $\alpha 4\beta 2^*$ -containing nicotinic receptors on thalamocortical terminals strongly facilitate thalamic excitation of layer V pyramidal neurons [139–141], an indirect effect that translates into a large increase in the frequency of rapid, glutamatergic excitatory postsynaptic currents. Of note, a positive feedback relationship has been demonstrated between nicotinic-elicited prefrontal glutamatergic release and the release of acetylcholine itself from cholinergic terminals in prefrontal cortex [97, 98, 142]. Nicotinic receptors have also been implicated in the modulation of monoamine release in the prefrontal cortex [143–145].

Nicotinic modulation of prefrontal GABAergic interneurons also likely contributes to attentional processing. Although  $\alpha 4\beta 2^*$ - and  $\alpha 7$ -containing nicotinic receptors excite only limited subpopulations of interneurons in the cerebral cortex [146, 147], many layer-specific effects have been documented. In layer VI, fast-spiking interneurons are excited indirectly by nicotinic stimulation [36], presumably due to innervation by corticothalamic axon collaterals [101]. In layer V, stimulation of nicotinic receptors on GABAergic interneurons increases the frequency of inhibitory postsynaptic currents on pyramidal neurons [148, 149], promotes intracolumnar inhibition [150], and modulates spike timing-dependent synaptic plasticity [149]. Most pyramidal neurons in layer II/III do not contain nicotinic receptors, nor do they receive glutamatergic inputs subject to nicotinic modulation ([61], but see [151,

152]). Instead, nicotinic receptors are found on interneurons that exert feedforward inhibition onto layer II/III pyramidal cells [61]. Nicotinic stimulation of the superficial layer I interneurons enhances synchronous activity of inhibitory cortical networks in superficial cortex [153, 154].

### Nicotinic receptor and prefrontal attention circuitry in health and disease

The prefrontal cortex is a critical node in widespread and dynamic brain networks that sustain higher cognitive function in health and that perpetuate executive dysfunction in psychiatric illness [155, 156]. The cholinergic modulation of prefrontal cortex is especially powerful in its ability to subsequently influence downstream cortical and subcortical networks [4, 157, 158], as well as being uniquely positioned to exert feedback control on neuromodulatory centers [159], including the cholinergic nuclei [160, 161]. Neuroimaging studies have revealed that the prefrontal cortex is consistently activated on attention tasks, often in conjunction with the parietal cortex [162–165], which is recruited by the prefrontal cortex under conditions of increased attentional demand [157].

A substantial body of work addresses the effects of acetylcholine on attention by manipulating endogenous levels of acetylcholine and by pharmacologically or genetically altering nicotinic acetylcholine receptors. Indeed, many genetic and pharmacological studies using both animal models and human subjects have found that nicotinic acetylcholine receptors are of particular importance for attention, as summarized in Table 2. Knockout mouse strains for the  $\alpha 5$ ,  $\beta 2$ , and  $\alpha 7$  nicotinic receptor subunits have all been found to display impaired attention performance on the 5-CSRTT [37, 38, 166, 167], and human subjects expressing genetic variations in the  $\alpha 5$ ,  $\alpha 4$ , or  $\beta 2$  genes are associated with increased risk for nicotine dependence [168–174], which may in part develop as a result of attention deficits that promote early experimentation with drugs and alcohol [168, 170, 172]. Pharmacologically, various nicotinic agonists have been found to improve attention performance in animal studies [175–180], whereas nicotinic antagonists appear to disrupt attention [178, 181]. However, it is important to note that the effects of nicotine may depend on the history of nicotine exposure [182] and on strain/species differences [37, 183].

The agonist nicotine is an interesting example since it is selective for nicotinic receptors and has been used in a large number of animal and human studies. Overall, the effects of nicotine in humans are far more complex and controversial, with inconsistent effects on attention performance

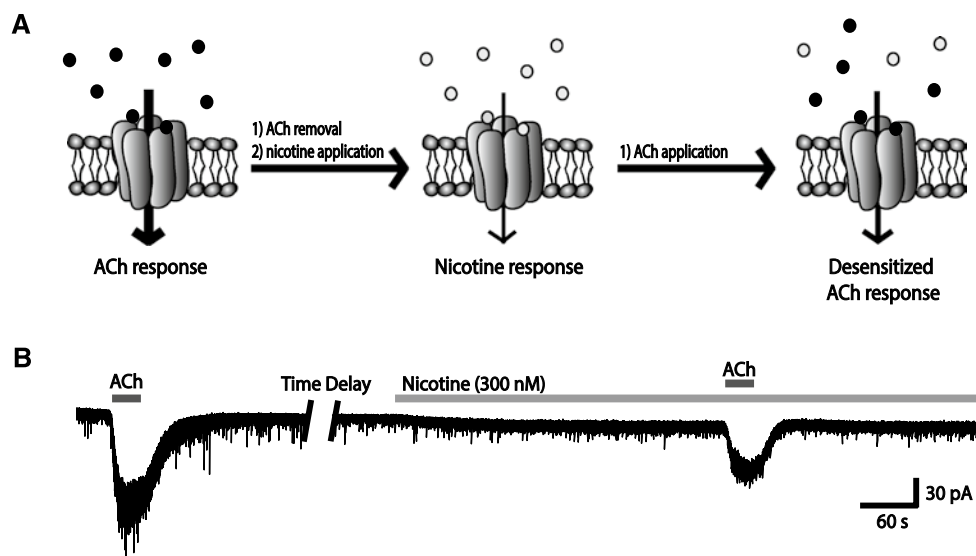
**Table 2** Nicotinic receptor effects on attention

Manipulation	Species	Task	Effects on attention	References
<b>Genetic studies</b>				
$\alpha 5$ subunit KO	Mice	5-CSRTT	↓	[37]
$\beta 2$ subunit KO	Mice	5-CSRTT	↓	[38]
$\alpha 7$ subunit KO	Mice	5-CSRTT	↓	[166, 167, 234]
	Mice	5-CSRTT	–	[38]
<b>Human polymorphisms</b> (arrow indicates effect of the risk allele)				
$\alpha 5$ subunit	Humans	Selective and sustained attention (CPT)	↓	[168]
		n-back/CPT	↓	[235]
$\alpha 4$ subunit	Humans	ADHD inattentive symptoms	↓	[236]
		Cued visual search task	↓	[237]
		Selective and sustained attention (CPT)	↓	[168]
		Multiple object tracking and visual search	↓	[238]
$\beta 2$ subunit	Humans	Selective attention (CPT)	↓	[168]
$\alpha 7$ subunit	Humans	Sustained attention (CPT)	↑ in smokers ↓ in nonsmokers	[168]
<b>Lesion studies</b>				
Basal forebrain lesions	Rats	5-CSRTT	↓	[13, 176, 239, 240]
Nucleus basalis of Meynert lesions	Rats	5-CSRTT	↓	[28, 31, 32]
mPFC lesions	Rats	5-CSRTT	↓	[241, 242]
mPFC lesions	Rats	Attentional set-shifting	↓	[243]
Lesions of PFC cholinergic fibers	Rats	5-CSRTT	↓	[17]
Lesions of PFC cholinergic fibers	Rats	SAT/dSAT	↓	[18]
<b>Pharmacological studies</b>				
<i>Nicotine</i> (agonist of nicotinic receptors, but act as an antagonist by desensitization)				
Nicotine	Monkeys	Covert orienting	↑	[244]
Nicotine	Monkeys	DMTS-D	↑	[175]
Nicotine	Rats	5-CSRTT	↑	[245]
Nicotine	Rats	5-CSRTT	–	[246]
Nicotine	Rats	Stimulus detection	↑	[178, 247–249]
Nicotine	Rats	5-CSRTT	↑	[180, 182, 250–253]
Nicotine	Rats (two strains)	5-CSRTT	↑ in Sprague–Dawley –in Lister	[177]
Nicotine	Rats	5-CSRTT	–(acute), ↑ (chronic)	[182]
Nicotine (local to HIP or mPFC)	Rats	5-CSRTT	–(HIP), ↑ (mPFC)	[180]
Nicotine	Mice	5-CSRTT	↑	[234]
Nicotine (local to mPFC)	Rats	3-CSRTT	↑ (mPFC)	[141]
Nicotine	Rats	5-CSRTT	↑ (acute and chronic)	[254]
Nicotine	Mice (three strains)	5-CSRTT	–(acute)	[183]
			↑ (chronic) in all strains	
Nicotine	Mice	5-CSRTT	↓	[37]
Nicotine	Rats	SAT	↓	[98]
Nicotine	Rats	Attention set-shifting	↑ (acute and sub-chronic)	[255]
Nicotine	Mice	5-CSRTT	↑	[256]
Nicotine (tablets)	Humans	Rapid info processing	↑	[186]

**Table 2** continued

Manipulation	Species	Task	Effects on attention	References
Nicotine (gum)	Humans	Two-letter/digit recall	↓	[191, 193]
Nicotine (subcutaneous)	Humans	Reaction time	–	[189]
Nicotine (subcutaneous)	Humans	Digit recall	↓	[192]
Nicotine (patch)	Humans	POMS/CPT/Digit recall	↑	[188]
Nicotine (gum)	Humans	Flight simulator	↑	[187]
Nicotine (patch)	Humans	Digit recall	–	[257]
Nicotine (patch)	Humans	Covert orienting	–	[258]
Nicotine (subcutaneous)	Humans	N-back	↑	[162]
Nicotine (gum)	Humans	ANT	–	[190]
Nicotine (gum)	Humans	Cue target detection	↑	[259]
Nicotine (gum)	Humans	Discrimination (Posner-type)	–	[260]
Nicotine (patch)	Humans	Stroop	–	[261]
Nicotine (gum)	Humans	Discrimination (Posner-type)	↑	[262, 263]
Nicotine (patch)	Humans	Multiple tasks	↑	[264]
Nicotine (gum)	Humans	RVIP	↑	[265]
Nicotine (patch)	Humans	Stroop/ANT	↑ (Stroop), ↓ (ANT)	[266]
Nicotine (intranasal)	Humans	CPT	↑	[267]
<i>Agonists of nicotinic receptors</i>				
ABT-418/ABT-089	Rats	DMTS-D	↑	[175, 176]
SIB-1533A	Rats	5-CSRTT	–	[250]
Dizocilpine then SIB-1533A	Rats	5-CSRTT	↓ (diz), attenuation with SIB	[268]
SIB-1533A	Monkeys	DMTS-D	↑	[268]
Epibatidine/ABT-418/isoarecolone/AR-R 17779	Rats	5-CSRTT	↑ (epi, ABT, iso), –(AR-R)	[180]
ABT-594/ABT-582941	Monkeys	DMTS-D	↑ (ABT-594, ABT-582941)	[269]
R3487/galanthamine	Rats	Signal detection	↑ (R3487), –(gal)	[270]
S 38232	Rats	SAT/dSAT	↑	[98]
ABT-594	Rats	5-CSRTT	↑	[271]
Dizocilpine/scopolamine then sazetidine-A	Rats	Signal detection	↓ (diz, sco), attenuation with saz	[179]
ABT-418	Mouse	5-CSRTT	↑	[256]
PNU 282987	Mouse	5-CSRTT	–	[256]
<i>Antagonists of nicotinic receptors</i>				
Mecamylamine	Rats	5-CSRTT	↓	[272]
Mecamylamine/hexamethonium	Rats	5-CSRTT	↓ (mec), –(hex)	[273]
Mecamylamine	Rats	Signal detection	↓	[178, 248]
Mecamylamine	Mice	5-CSRTT	↓ (mec) in three strains	[183]
Mecamylamine	Humans	Digit vigilance, RVIP	–(mec)	[274]
<i>Acetylcholinesterase inhibitors</i>				
Physostigmine	Rats	5-CSRTT	–	[272]
Donepezil	Humans	Flight simulator	↑	[275]
Donepezil	Humans	Anti-cueing	↑ (voluntary attention only)	[276]
<i>Acetylcholine reuptake blockers</i>				
Hemicholinium	Rats	5-CSRTT	↓	[13]

**Fig. 7** A concentration of nicotine similar to that seen in the blood of smokers markedly reduces subsequent nicotinic receptor-mediated responses to acetylcholine (ACh). **a** Schematic of the acetylcholine response, nicotine response, and acetylcholine response following receptor desensitization by nicotine. **b** Representative whole-cell recordings of a layer VI pyramidal neurons showing: (1) an initial response to ACh, (2) response to nicotine, and (3) response to ACh following desensitization by nicotine. Figure adapted from Bailey et al. [37]



[184, 185]. While nicotine has also been shown to improve attention in humans [186–188], this is not always the case [189–193]. Evidence suggests that nicotine may have differential effects in human smoker and non-smoker populations [185, 194–196], and in patients with attention deficits [197, 198].

At the cellular level, nicotinic receptors are subject to desensitization; that is, they can become temporarily inactive in the continued presence of agonist, leading to a reduction in response [83, 84]. Nicotine, at levels normally seen in the blood of smokers (~300 nM) [199–201], can have such an effect on  $\alpha 4\beta 2^*$  receptors [36, 37], as illustrated in Fig. 7. Interestingly, Bailey et al. [37] reported that the  $\alpha 5$  subunit normally protects against nicotine-induced desensitization, since layer VI neurons from WT mice show half as much desensitization as those of  $\alpha 5^{-/-}$  mice. The low-affinity  $\alpha 7^*$  nicotinic acetylcholine receptors, on the other hand, do not appear to desensitize at these concentrations [202].

Deficits in attention have been reported in normal human aging [203] as well as a multitude of neurological and psychiatric disorders, such as Alzheimer's disease and schizophrenia [204–207]. Decreases in prefrontal nicotinic receptor binding are observed in patients suffering from mild cognitive impairment [208, 209] as well as Alzheimer's disease [210–215], and schizophrenia has been associated both with  $\alpha 7$  subunit polymorphisms and expression changes [216, 217], as well as with a higher incidence of the noncoding  $\alpha 5$  nicotinic subunit polymorphism [218, 219]. What is more, nicotinic agonists of the  $\alpha 4\beta 2^*$  and  $\alpha 7$  nicotinic receptors have been proposed as potential therapeutics for schizophrenia [220], Alzheimer's disease [221–224], and attention deficit hyperactivity disorder [225–229].

## In conclusion

Layer VI nicotinic receptors are integral components of prefrontal attention circuitry in development and adulthood. Despite recent advances, there remains much to be understood about their effects on the maturation of the prefrontal cortex and the modulation of its neurons and networks. Fundamental questions about the regulation of nicotinic receptors in neurons of the living brain remain unanswered. An apparently large reserve of nicotinic receptors within layer VI prefrontal neurons [63, 92], for example, suggests the potential for targeted upregulation to the membrane [230, 231]. It is interesting to note that nicotinic receptor trafficking abnormalities have been documented in psychiatric illness [232]. The issue of physiological and structural plasticity [59, 63] further suggests that the brain may be fundamentally different in certain conditions, and the best treatments may not be those that would improve the performance of the normal brain. In this regard, it is essential for research to examine the realities of prefrontal attention circuitry in different conditions associated with attention deficits. These issues are all the more important to resolve given that nicotinic receptors in layer VI of prefrontal cortex are positioned to be potential drug targets in the treatment of the attention deficits associated with psychiatric and neurological diseases [233].

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## References

- Crick F (1984) Function of the thalamic reticular complex: the searchlight hypothesis. *PNAS* 81:4586–4590
- Knudsen EI (2007) Fundamental components of attention. *Annu Rev Neurosci* 30:57–78. doi:10.1146/annurev.neuro.30.051606.094256
- Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. *Annu Rev Neurosci* 24:167–202. doi:10.1146/annurev.neuro.24.1.167
- Funahashi S (2001) Neuronal mechanisms of executive control by the prefrontal cortex. *Neurosci Res* 39:147–165
- Baddeley A (1992) Working memory. *Science* 255:556–559
- Dehaene S, Changeux J-P (2011) Experimental and theoretical approaches to conscious processing. *Neuron* 70:200–227. doi:10.1016/j.neuron.2011.03.018
- Petersen SE, Posner MI (2012) The attention system of the human brain: 20 years after. *Annu Rev Neurosci* 35:73–89. doi:10.1146/annurev-neuro-062111-150525
- Deutsch JA, Rocklin KW (1967) Amnesia induced by scopolamine and its temporal variations. *Nature* 216:89–90. doi:10.1038/216089b0
- Deutsch JA (1971) The cholinergic synapse and the site of memory. *Science* 174:788–794
- Warburton DM, Brown K (1971) Attenuation of stimulus sensitivity induced by scopolamine. *Nature* 230:126–127. doi:10.1038/230126a0
- Robbins TW, Everitt BJ, Marston HM et al (1989) 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 of the nucleus basalis in cognitive processes. *Behav Brain Res* 35:221–240
- Dunnett SB, Everitt BJ, Robbins TW (1991) The basal forebrain-cortical cholinergic system: interpreting the functional consequences of excitotoxic lesions. *Trends Neurosci* 14:494–501
- Muir JL, Dunnett SB, Robbins TW, Everitt BJ (1992) Attentional functions of the forebrain cholinergic systems: effects of intraventricular hemicholinium, physostigmine, basal forebrain lesions and intracortical grafts on a multiple-choice serial reaction time task. *Exp Brain Res* 89:611–622
- Muir JL, Page KJ, Sirinathsinghji DJ et al (1993) Excitotoxic lesions of basal forebrain cholinergic neurons: effects on learning, memory and attention. *Behav Brain Res* 57:123–131
- Pang K, Williams MJ, Egeth H, Olton DS (1993) Nucleus basalis magnocellularis and attention: effects of muscimol infusions. *Behav Neurosci* 107:1031–1038
- Voytko ML, Olton DS, Richardson RT et al (1994) Basal forebrain lesions in monkeys disrupt attention but not learning and memory. *J Neurosci* 14:167–186
- Dalley JW, Theobald DE, Bouger P et al (2004) Cortical cholinergic function and deficits in visual attentional performance in rats following 192 IgG-saporin-induced lesions of the medial prefrontal cortex. *Cereb Cortex* 14:922–932. doi:10.1093/cercor/bhh052
- Newman LA, McGaughy J (2008) Cholinergic deafferentation of prefrontal cortex increases sensitivity to cross-modal distractors during a sustained attention task. *J Neurosci* 28:2642–2650. doi:10.1523/JNEUROSCI.5112-07.2008
- Bigl V, Woolf NJ, Butcher LL (1982) Cholinergic projections from the basal forebrain to frontal, parietal, temporal, occipital, and cingulate cortices: a combined fluorescent tracer and acetylcholinesterase analysis. *Brain Res Bull* 8:727–749
- Mesulam MM, Mufson EJ, Wainer BH, Levey AI (1983) Central cholinergic pathways in the rat: an overview based on an alternative nomenclature (Ch1–Ch6). *Neuroscience* 10:1185–1201
- Mesulam MM, Mufson EJ, Levey AI, Wainer BH (1983) Cholinergic innervation of cortex by the basal forebrain: cytochemistry and cortical connections of the septal area, diagonal band nuclei, nucleus basalis (Substantia innominata), and hypothalamus in the rhesus monkey. *J Comp Neurol* 214:170–197. doi:10.1002/cne.902140206
- Woolf NJ, Eckenstein F, Butcher LL (1983) Cholinergic projections from the basal forebrain to the frontal cortex: a combined fluorescent tracer and immunohistochemical analysis in the rat. *Neurosci Lett* 40:93–98
- Rye DB, Wainer BH, Mesulam MM et al (1984) Cortical projections arising from the basal forebrain: a study of cholinergic and noncholinergic components employing combined retrograde tracing and immunohistochemical localization of choline acetyltransferase. *Neuroscience* 13:627–643. doi:10.1016/0306-4522(84)90083-6
- Lewis DA (1991) Distribution of choline acetyltransferase-immunoreactive axons in monkey frontal cortex. *Neuroscience* 40:363–374
- Woolf NJ (1991) Cholinergic systems in mammalian brain and spinal cord. *Prog Neurobiol* 37:475–524
- Mrzjak L, Pappy M, Leranth C, Goldman-Rakic PS (1995) Cholinergic synaptic circuitry in the-1. *J Comp Neurol* 357:603–617. doi:10.1002/cne.903570409
- McGaughy J, Kaiser T, Sarter M (1996) 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* 110:247–265
- McGaughy J, Dalley JW, Morrison CH et al (2002) Selective behavioral and neurochemical effects of cholinergic lesions produced by intrabasalis infusions of 192 IgG-saporin on attentional performance in a five-choice serial reaction time task. *J Neurosci* 22:1905–1913
- Parikh V, Kozak R, Martinez V, Sarter M (2007) Prefrontal acetylcholine release controls cue detection on multiple timescales. *Neuron* 56:141–154. doi:10.1016/j.neuron.2007.08.025
- Passetti F, Dalley JW, O'Connell MT et al (2000) Increased acetylcholine release in the rat medial prefrontal cortex during performance of a visual attentional task. *Eur J Neurosci* 12:3051–3058
- Dalley JW, McGaughy J, O'Connell MT et al (2001) Distinct changes in cortical acetylcholine and noradrenaline efflux during contingent and noncontingent performance of a visual attentional task. *J Neurosci* 21:4908–4914
- Himmelheber AM, Sarter M, Bruno JP (2000) Increases in cortical acetylcholine release during sustained attention performance in rats. *Brain Res Cogn Brain Res* 9:313–325
- Kozak R, Bruno JP, Sarter M (2006) Augmented prefrontal acetylcholine release during challenged attentional performance. *Cereb Cortex* 16:9–17. doi:10.1093/cercor/bhi079
- Sarter M, Gehring WJ, Kozak R (2006) More attention must be paid: the neurobiology of attentional effort. *Brain Res Rev* 51:145–160. doi:10.1016/j.brainresrev.2005.11.002
- Howe WM, Berry AS, Francois J et al (2013) Prefrontal cholinergic mechanisms instigating shifts from monitoring for cues to cue-guided performance: converging electrochemical and fMRI evidence from rats and humans. *J Neurosci* 33:8742–8752. doi:10.1523/JNEUROSCI.5809-12.2013

36. Kassam SM, Herman PM, Goodfellow NM et al (2008) Developmental excitation of corticothalamic neurons by nicotinic acetylcholine receptors. *J Neurosci* 28:8756–8764. doi:[10.1523/JNEUROSCI.2645-08.2008](https://doi.org/10.1523/JNEUROSCI.2645-08.2008)
37. Bailey CDC, De Biasi M, Fletcher PJ, Lambe EK (2010) The nicotinic acetylcholine receptor alpha5 subunit plays a key role in attention circuitry and accuracy. *J Neurosci* 30:9241–9252. doi:[10.1523/JNEUROSCI.2258-10.2010](https://doi.org/10.1523/JNEUROSCI.2258-10.2010)
38. Guillem K, Bloem B, Poorthuis RB et al (2011) Nicotinic acetylcholine receptor beta2 subunits in the medial prefrontal cortex control attention. *Science* 333:888–891. doi:[10.1126/science.1207079](https://doi.org/10.1126/science.1207079)
39. Sarter M, Paolone G (2011) Deficits in attentional control: cholinergic mechanisms and circuitry-based treatment approaches. *Behav Neurosci* 125:825–835. doi:[10.1037/a0026227](https://doi.org/10.1037/a0026227)
40. Sarter M, Givens B, Bruno JP (2001) The cognitive neuroscience of sustained attention: where top-down meets bottom-up. *Brain Res Brain Res Rev* 35:146–160
41. Sarter M, Hasselmo ME, Bruno JP, Givens B (2005) Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. *Brain Res Brain Res Rev* 48:98–111. doi:[10.1016/j.brainresrev.2004.08.006](https://doi.org/10.1016/j.brainresrev.2004.08.006)
42. Thomson AM (2010) Neocortical layer 6, a review. *Front Neuroanat* 4:13. doi:[10.3389/fnana.2010.00013](https://doi.org/10.3389/fnana.2010.00013)
43. Alitto HJ, Usrey WM (2003) Corticothalamic feedback and sensory processing. *Curr Opin Neurobiol* 13:440–445
44. Gabbott PL, Warner TA, Jays PR et al (2005) Prefrontal cortex in the rat: projections to subcortical autonomic, motor, and limbic centers. *J Comp Neurol* 492:145–177. doi:[10.1002/cne.20738](https://doi.org/10.1002/cne.20738)
45. Zikopoulos B, Barbas H (2006) Prefrontal projections to the thalamic reticular nucleus form a unique circuit for attentional mechanisms. *J Neurosci* 26:7348–7361. doi:[10.1523/JNEUROSCI.5511-05.2006](https://doi.org/10.1523/JNEUROSCI.5511-05.2006)
46. Briggs F, Usrey WM (2011) Corticogeniculate feedback and visual processing in the primate. *J Physiol-London* 589:33–40. doi:[10.1113/jphysiol.2010.193599](https://doi.org/10.1113/jphysiol.2010.193599)
47. Cudeiro J, Sillito AM (2006) Looking back: corticothalamic feedback and early visual processing. *Trends Neurosci* 29:298–306. doi:[10.1016/j.tins.2006.05.002](https://doi.org/10.1016/j.tins.2006.05.002)
48. Sherman SM (2007) The thalamus is more than just a relay. *Curr Opin Neurobiol* 17:417–422. doi:[10.1016/j.conb.2007.07.003](https://doi.org/10.1016/j.conb.2007.07.003)
49. Zhang L, Jones EG (2004) Corticothalamic inhibition in the thalamic reticular nucleus. *J Neurophysiol* 91:759–766. doi:[10.1152/jn.00624.2003](https://doi.org/10.1152/jn.00624.2003)
50. von Krosigk M, Monckton JE, Reiner PB, McCormick DA (1999) Dynamic properties of corticothalamic excitatory postsynaptic potentials and thalamic reticular inhibitory postsynaptic potentials in thalamocortical neurons of the guinea-pig dorsal lateral geniculate nucleus. *Neuroscience* 91:7–20
51. Destexhe A (2000) Modelling corticothalamic feedback and the gating of the thalamus by the cerebral cortex. *J Physiol Paris* 94:391–410
52. Smythies J (1997) The functional neuroanatomy of awareness: with a focus on the role of various anatomical systems in the control of intermodal attention. *Conscious Cogn* 6:455–481. doi:[10.1006/ccog.1997.0315](https://doi.org/10.1006/ccog.1997.0315)
53. Guillery RW, Sherman SM (2002) Thalamic relay functions and their role in corticocortical communication: generalizations from the visual system. *Neuron* 33:163–175
54. Van der Werf Y, Witter M, Groenewegen H (2002) The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Res Rev* 39:107–140
55. Berendse HW, Groenewegen HJ (1991) Restricted cortical termination fields of the midline and intralaminar thalamic nuclei in the rat. *Neuroscience* 42:73–102
56. Hoover WB, Vertes RP (2007) Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. *Brain Struct Funct* 212:149–179. doi:[10.1007/s00429-007-0150-4](https://doi.org/10.1007/s00429-007-0150-4)
57. Vertes RP (2006) Interactions among the medial prefrontal cortex, hippocampus and midline thalamus in emotional and cognitive processing in the rat. *Neuroscience* 142:1–20. doi:[10.1016/j.neuroscience.2006.06.027](https://doi.org/10.1016/j.neuroscience.2006.06.027)
58. Dempsey EW, Morison RS (1942) The electrical activity of a thalamocortical relay system. *Am J Physiol* 138:283–296
59. Tian MK, Bailey CDC, De Biasi M et al (2011) Plasticity of prefrontal attention circuitry: upregulated muscarinic excitability in response to decreased nicotinic signaling following deletion of  $\alpha 5$  or  $\beta 2$  subunits. *J Neurosci* 31:16458–16463. doi:[10.1523/JNEUROSCI.3600-11.2011](https://doi.org/10.1523/JNEUROSCI.3600-11.2011)
60. Olsen SR, Bortone DS, Adesnik H, Scanziani M (2012) Gain control by layer six in cortical circuits of vision. *Nature* 482:47–52. doi:[10.1038/nature10835](https://doi.org/10.1038/nature10835)
61. Poorthuis RB, Bloem B, Schak B et al (2012) Layer-specific modulation of the prefrontal cortex by nicotinic acetylcholine receptors. *Cereb Cortex* 23:148–161. doi:[10.1093/cercor/bhr390](https://doi.org/10.1093/cercor/bhr390)
62. Henny P, Jones BE (2008) Projections from basal forebrain to prefrontal cortex comprise cholinergic, GABAergic and glutamatergic inputs to pyramidal cells or interneurons. *Eur J Neurosci* 27:654–670. doi:[10.1111/j.1460-9568.2008.06029.x](https://doi.org/10.1111/j.1460-9568.2008.06029.x)
63. Bailey CDC, Alves NC, Nashmi R et al (2012) Nicotinic  $\alpha 5$  subunits drive developmental changes in the activation and morphology of prefrontal cortex layer VI neurons. *Biol Psychiatry* 71:120–128. doi:[10.1016/j.biopsych.2011.09.011](https://doi.org/10.1016/j.biopsych.2011.09.011)
64. Houser CR, Crawford GD, Salvaterra PM, Vaughn JE (1985) Immunocytochemical localization of choline acetyltransferase in rat cerebral cortex: a study of cholinergic neurons and synapses. *J Comp Neurol* 234:17–34. doi:[10.1002/cne.902340103](https://doi.org/10.1002/cne.902340103)
65. Gotti C, Clementi F, Fornari A et al (2009) Structural and functional diversity of native brain neuronal nicotinic receptors. *Biochem Pharmacol* 78:703–711. doi:[10.1016/j.bcp.2009.05.024](https://doi.org/10.1016/j.bcp.2009.05.024)
66. Albuquerque EX, Pereira EFR, Alkondon M, Rogers SW (2009) Mammalian nicotinic acetylcholine receptors: from structure to function. *Physiol Rev* 89:73–120. doi:[10.1152/physrev.00015.2008](https://doi.org/10.1152/physrev.00015.2008)
67. Fucile S (2004)  $Ca^{2+}$  permeability of nicotinic acetylcholine receptors. *Cell Calcium* 35:1–8
68. Lindstrom J (2000) The structures of neuronal nicotinic receptors. In: *Neuronal nicotinic receptors*. Springer, Berlin/Heidelberg, pp 101–162
69. Moroni M, Zwart R, Sher E et al (2006)  $\alpha 4\beta 2$  nicotinic receptors with high and low acetylcholine sensitivity: pharmacology, stoichiometry, and sensitivity to long-term exposure to nicotine. *Mol Pharmacol* 70:755–768. doi:[10.1124/mol.106.023044](https://doi.org/10.1124/mol.106.023044)
70. Marks MJ, Meinerz NM, Brown RWB, Collins AC (2010)  $86Rb^{+}$  efflux mediated by  $\alpha 4\beta 2^{*}$ -nicotinic acetylcholine receptors with high and low-sensitivity to stimulation by acetylcholine display similar agonist-induced desensitization. *Biochem Pharmacol* 80:1238–1251. doi:[10.1016/j.bcp.2010.06.040](https://doi.org/10.1016/j.bcp.2010.06.040)
71. Tapia L, Kuryatov A, Lindstrom J (2007)  $Ca^{2+}$  permeability of the  $(\alpha 4)_3(\beta 2)_2$  stoichiometry greatly exceeds that of  $(\alpha 4)_2(\beta 2)_3$  human acetylcholine receptors. *Mol Pharmacol* 71:769–776. doi:[10.1124/mol.106.030445](https://doi.org/10.1124/mol.106.030445)
72. Grady SR, Wageman CR, Patzlaff NE, Marks MJ (2012) Low concentrations of nicotine differentially desensitize nicotinic acetylcholine receptors that include  $\alpha 5$  or  $\alpha 6$  subunits and that

- mediate synaptosomal neurotransmitter release. *Neuropharmacology* 62:1935–1943. doi:[10.1016/j.neuropharm.2011.12.026](https://doi.org/10.1016/j.neuropharm.2011.12.026)
73. Ferreira M, Ebert SN, Perry DC et al (2001) Evidence of a functional alpha7-neuronal nicotinic receptor subtype located on motoneurons of the dorsal motor nucleus of the vagus. *J Pharmacol Exp Ther* 296:260–269
  74. Léna C, Changeux J-P (1999) The role of beta2-subunit-containing nicotinic acetylcholine receptors in the brain explored with a mutant mouse. *Ann N Y Acad Sci* 868:611–616
  75. Perry DC, Xiao Y, Nguyen HN et al (2002) Measuring nicotinic receptors with characteristics of alpha4beta2, alpha3beta2 and alpha3beta4 subtypes in rat tissues by autoradiography. *J Neurochem* 82:468–481
  76. Wada E, Wada K, Boulter J et al (1989) Distribution of alpha2, alpha3, alpha4, and beta2 neuronal nicotinic receptor subunit mRNAs in the central nervous system: a hybridization histochemical study in the rat. *J Comp Neurol* 284:314–335. doi:[10.1002/cne.902840212](https://doi.org/10.1002/cne.902840212)
  77. Hill JA, Zoli M, Bourgeois JP, Changeux J-P (1993) Immunocytochemical localization of a neuronal nicotinic receptor: the beta2-subunit. *J Neurosci* 13:1551–1568
  78. Nakayama H, Shioda S, Okuda H et al (1995) Immunocytochemical localization of nicotinic acetylcholine receptor in rat cerebral cortex. *Brain Res Mol Brain Res* 32:321–328
  79. Gotti C, Clementi F (2004) Neuronal nicotinic receptors: from structure to pathology. *Prog Neurobiol* 74:363–396. doi:[10.1016/j.pneurobio.2004.09.006](https://doi.org/10.1016/j.pneurobio.2004.09.006)
  80. Dominguez del Toro E, Juiz JM, Peng X et al (1994) Immunocytochemical localization of the alpha 7 subunit of the nicotinic acetylcholine receptor in the rat central nervous system. *J Comp Neurol* 349:325–342. doi:[10.1002/cne.903490302](https://doi.org/10.1002/cne.903490302)
  81. Han ZY, Le Novère N, Zoli M et al (2000) Localization of nAChR subunit mRNAs in the brain of *Macaca mulatta*. *Eur J Neurosci* 12:3664–3674
  82. Gotti C, Zoli M, Clementi F (2006) Brain nicotinic acetylcholine receptors: native subtypes and their relevance. *Trends Pharmacol Sci* 27:482–491. doi:[10.1016/j.tips.2006.07.004](https://doi.org/10.1016/j.tips.2006.07.004)
  83. Giniatullin R, Nistri A, Yakel JL (2005) Desensitization of nicotinic ACh receptors: shaping cholinergic signaling. *Trends Neurosci* 28:371–378. doi:[10.1016/j.tins.2005.04.009](https://doi.org/10.1016/j.tins.2005.04.009)
  84. Quick MW, Lester RAJ (2002) Desensitization of neuronal nicotinic receptors. *J Neurobiol* 53:457–478. doi:[10.1002/neu.10109](https://doi.org/10.1002/neu.10109)
  85. Conroy WG, Vernallis AB, Berg DK (1992) The alpha5 gene product assembles with multiple acetylcholine receptor subunits to form distinctive receptor subtypes in brain. *Neuron* 9:679–691
  86. Wada E, McKinnon D, Heinemann S et al (1990) The distribution of mRNA encoded by a new member of the neuronal nicotinic acetylcholine receptor gene family (alpha5) in the rat central nervous system. *Brain Res* 526:45–53
  87. Ramirez-Latorre J, Yu CR, Qu X et al (1996) Functional contributions of alpha5 subunit to neuronal acetylcholine receptor channels. *Nature* 380:347–351. doi:[10.1038/380347a0](https://doi.org/10.1038/380347a0)
  88. Kuryatov A, Onksen J, Lindstrom J (2008) Roles of accessory subunits in alpha4beta2(\*) nicotinic receptors. *Mol Pharmacol* 74:132–143. doi:[10.1124/mol.108.046789](https://doi.org/10.1124/mol.108.046789)
  89. Mao D, Perry DC, Yasuda RP et al (2008) The alpha4beta2alpha5 nicotinic cholinergic receptor in rat brain is resistant to up-regulation by nicotine in vivo. *J Neurochem* 104:446–456. doi:[10.1111/j.1471-4159.2007.05011.x](https://doi.org/10.1111/j.1471-4159.2007.05011.x)
  90. McClure-Begley TD, King NM, Collins AC et al (2009) Acetylcholine-stimulated [3H]GABA release from mouse brain synaptosomes is modulated by alpha4beta2 and alpha4alpha5beta2 nicotinic receptor subtypes. *Mol Pharmacol* 75:918–926. doi:[10.1124/mol.108.052274](https://doi.org/10.1124/mol.108.052274)
  91. Grady SR, Salminen O, McIntosh JM et al (2010) Mouse striatal dopamine nerve terminals express alpha4alpha5beta2 and two stoichiometric forms of alpha4beta2\*-nicotinic acetylcholine receptors. *J Mol Neurosci* 40:91–95. doi:[10.1007/s12031-009-9263-y](https://doi.org/10.1007/s12031-009-9263-y)
  92. Alves NC, Bailey CDC, Nashmi R, Lambe EK (2010) Developmental sex differences in nicotinic currents of prefrontal layer VI neurons in mice and rats. *PLoS ONE* 5:e9261. doi:[10.1371/journal.pone.0009261](https://doi.org/10.1371/journal.pone.0009261)
  93. Marks MJ, Pauly JR, Gross SD et al (1992) Nicotine binding and nicotinic receptor subunit RNA after chronic nicotine treatment. *J Neurosci* 12:2765–2784
  94. Salas R, Orr-Urtreger A, Broide RS et al (2003) The nicotinic acetylcholine receptor subunit alpha5 mediates short-term effects of nicotine in vivo. *Mol Pharmacol* 63:1059–1066
  95. Winzer-Serhan UH, Leslie FM (2005) Expression of alpha5 nicotinic acetylcholine receptor subunit mRNA during hippocampal and cortical development. *J Comp Neurol* 481:19–30. doi:[10.1002/cne.20357](https://doi.org/10.1002/cne.20357)
  96. Brown RWB, Collins AC, Lindstrom JM, Whiteaker P (2007) Nicotinic alpha5 subunit deletion locally reduces high-affinity agonist activation without altering nicotinic receptor numbers. *J Neurochem* 103:204–215. doi:[10.1111/j.1471-4159.2007.04700.x](https://doi.org/10.1111/j.1471-4159.2007.04700.x)
  97. Parikh V, Man K, Decker MW, Sarter M (2008) Glutamatergic contributions to nicotinic acetylcholine receptor agonist-evoked cholinergic transients in the prefrontal cortex. *J Neurosci* 28:3769–3780. doi:[10.1523/JNEUROSCI.5251-07.2008](https://doi.org/10.1523/JNEUROSCI.5251-07.2008)
  98. Howe WM, Ji J, Parikh V et al (2010) Enhancement of attentional performance by selective stimulation of alpha4beta2(\*) nAChRs: underlying cholinergic mechanisms. *Neuropsychopharmacol* 35:1391–1401. doi:[10.1038/npp.2010.9](https://doi.org/10.1038/npp.2010.9)
  99. A Mathie DCSGC-C (1990) Rectification of currents activated by nicotinic acetylcholine receptors in rat sympathetic ganglion neurones. *J Physiol* 427:625
  100. Forster I, Bertrand D (1995) Inward rectification of neuronal nicotinic acetylcholine receptors investigated by using the homomeric alpha7 receptor. *Proc Biol Sci* 260:139–148. doi:[10.1098/rspb.1995.0071](https://doi.org/10.1098/rspb.1995.0071)
  101. West DC, Mercer A, Kirchhecker S et al (2006) Layer 6 corticothalamic pyramidal cells preferentially innervate interneurons and generate facilitating EPSPs. *Cereb Cortex* 16:200–211. doi:[10.1093/cercor/bhi098](https://doi.org/10.1093/cercor/bhi098)
  102. Mercer A, West DC, Morris OT et al (2005) Excitatory connections made by presynaptic cortico-cortical pyramidal cells in layer 6 of the neocortex. *Cereb Cortex* 15:1485–1496. doi:[10.1093/cercor/bhi027](https://doi.org/10.1093/cercor/bhi027)
  103. Robbins TW (2002) The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. *Psychopharmacology* 163:362–380. doi:[10.1007/s00213-002-1154-7](https://doi.org/10.1007/s00213-002-1154-7)
  104. Sunderland T, Weingartner H, Cohen RM et al (1989) Low-dose oral lorazepam administration in Alzheimer subjects and age-matched controls. *Psychopharmacology* 99:129–133
  105. Foldi NS, Jutagir R, Davidoff D, Gould T (1992) Selective attention skills in Alzheimer's disease: performance on graded cancellation tests varying in density and complexity. *J Gerontol* 47:P146–P153
  106. Okonkwo OC, Wadley VG, Ball K et al (2008) Dissociations in visual attention deficits among persons with mild cognitive impairment. *Neuropsychol Dev Cogn B Aging Neuropsychol Cogn* 15:492–505. doi:[10.1080/13825580701844414](https://doi.org/10.1080/13825580701844414)
  107. Okonkwo OC, Crowe M, Wadley VG, Ball K (2008) Visual attention and self-regulation of driving among older adults. *Int Psychogeriatr* 20:162–173. doi:[10.1017/S104161020700539X](https://doi.org/10.1017/S104161020700539X)

108. Shaw P, Eckstrand K, Sharp W et al (2007) Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *PNAS* 104:19649–19654. doi:[10.1073/pnas.0707741104](https://doi.org/10.1073/pnas.0707741104)
109. Sullivan RM, Brake WG (2003) What the rodent prefrontal cortex can teach us about attention-deficit/hyperactivity disorder: the critical role of early developmental events on prefrontal function. *Behav Brain Res* 146:43–55
110. Krain AL, Castellanos FX (2006) Brain development and ADHD. *Clin Psychol Rev* 26:433–444. doi:[10.1016/j.cpr.2006.01.005](https://doi.org/10.1016/j.cpr.2006.01.005)
111. Nishimura A, Hohmann CF, Johnston MV, Blue ME (2002) Neonatal electrolytic lesions of the basal forebrain stunt plasticity in mouse barrel field cortex. *Int J Dev Neurosci* 20:481–489
112. Kuczewski N, Aztiria E, Leanza G, Domenici L (2005) Selective cholinergic immunolesioning affects synaptic plasticity in developing visual cortex. *Eur J Neurosci* 21:1807–1814. doi:[10.1111/j.1460-9568.2005.04014.x](https://doi.org/10.1111/j.1460-9568.2005.04014.x)
113. Robertson RT, Gallardo KA, Claytor KJ et al (1998) Neonatal treatment with 192 IgG-saporin produces long-term forebrain cholinergic deficits and reduces dendritic branching and spine density of neocortical pyramidal neurons. *Cereb Cortex* 8:142–155
114. Sherren N, Pappas BA (2005) Selective acetylcholine and dopamine lesions in neonatal rats produce distinct patterns of cortical dendritic atrophy in adulthood. *Neuroscience* 136:445–456. doi:[10.1016/j.neuroscience.2005.08.053](https://doi.org/10.1016/j.neuroscience.2005.08.053)
115. Heath CJ, Picciotto MR (2009) Nicotine-induced plasticity during development: modulation of the cholinergic system and long-term consequences for circuits involved in attention and sensory processing. *Neuropharmacology* 56(Suppl 1):254–262. doi:[10.1016/j.neuropharm.2008.07.020](https://doi.org/10.1016/j.neuropharm.2008.07.020)
116. Perry EK, Lee ML, Martin-Ruiz CM et al (2001) Cholinergic activity in autism: abnormalities in the cerebral cortex and basal forebrain. *Am J Psychiatry* 158:1058–1066
117. Martin-Ruiz CM, Lee M, Perry RH et al (2004) Molecular analysis of nicotinic receptor expression in autism. *Brain Res Mol Brain Res* 123:81–90. doi:[10.1016/j.molbrainres.2004.01.003](https://doi.org/10.1016/j.molbrainres.2004.01.003)
118. Picard F, Bruel D, Servent D et al (2006) Alteration of the in vivo nicotinic receptor density in ADNPLE patients: a PET study. *Brain* 129:2047–2060. doi:[10.1093/brain/awl156](https://doi.org/10.1093/brain/awl156)
119. Breese CR, Lee MJ, Adams CE et al (2000) Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. *Neuropsychopharmacol* 23:351–364. doi:[10.1016/S0893-133X\(00\)00121-4](https://doi.org/10.1016/S0893-133X(00)00121-4)
120. Marutle A, Zhang X, Court J et al (2001) Laminar distribution of nicotinic receptor subtypes in cortical regions in schizophrenia. *J Chem Neuroanat* 22:115–126
121. Kristt DA (1979) Acetylcholinesterase-containing neurons of layer VIB in immature neocortex: possible component of an early formed intrinsic cortical circuit. *Anat Embryol* 157:217–226
122. Mechawar N, Descarries L (2001) The cholinergic innervation develops early and rapidly in the rat cerebral cortex: a quantitative immunocytochemical study. *Neuroscience* 108:555–567
123. Romijn HJ, Hofman MA, Gramsbergen A (1991) At what age is the developing cerebral cortex of the rat comparable to that of the full-term newborn human baby? *Early Hum Dev* 26:61–67
124. Watson RE, Desesso JM, Hurtt ME, Cappon GD (2006) Postnatal growth and morphological development of the brain: a species comparison. *Birth Defect Res B* 77:471–484. doi:[10.1002/bdrb.20090](https://doi.org/10.1002/bdrb.20090)
125. Tribollet E, Bertrand D, Marguerat A, Raggenbass M (2004) Comparative distribution of nicotinic receptor subtypes during development, adulthood and aging: an autoradiographic study in the rat brain. *Neuroscience* 124:405–420. doi:[10.1016/j.neuroscience.2003.09.028](https://doi.org/10.1016/j.neuroscience.2003.09.028)
126. Cimino M, Marini P, Colombo S, et al (1995) Expression of neuronal acetylcholine nicotinic receptor  $\alpha 4$  and  $\beta 2$  subunits during postnatal development of the rat brain. *J Neural Transm* 100:77–92. doi:[10.1007/BF01271531](https://doi.org/10.1007/BF01271531)
127. Zhang X, Liu C, Miao H et al (1998) Postnatal changes of nicotinic acetylcholine receptor alpha2, alpha3, alpha4, alpha7 and beta2 subunits genes expression in rat brain. *Int J Dev Neurosci* 16:507–518
128. Lipton SA, Frosch MP, Phillips MD et al (1988) Nicotinic antagonists enhance process outgrowth by rat retinal ganglion cells in culture. *Science* 239:1293–1296
129. Pugh PC, Berg DK (1994) Neuronal acetylcholine receptors that bind alpha-bungarotoxin mediate neurite retraction in a calcium-dependent manner. *J Neurosci* 14:889–896
130. Bertrand D, Valera S, Bertrand S et al (1991) Steroids inhibit nicotinic acetylcholine receptors. *NeuroReport* 2:277–280
131. Valera S, Ballivet M, Bertrand D (1992) Progesterone modulates a neuronal nicotinic acetylcholine receptor. *PNAS* 89:9949–9953
132. Kohchi C, Ukena K, Tsutsui K (1998) Age- and region-specific expressions of the messenger RNAs encoding for steroidogenic enzymes p450scc, P450c17 and 3beta-HSD in the postnatal rat brain. *Brain Res* 801:233–238
133. Zwain IH, Yen SS (1999) Neurosteroidogenesis in astrocytes, oligodendrocytes, and neurons of cerebral cortex of rat brain. *Endocrinology* 140:3843–3852
134. Paradiso K, Zhang J, Steinbach JH (2001) The C terminus of the human nicotinic alpha4beta2 receptor forms a binding site required for potentiation by an estrogenic steroid. *J Neurosci* 21:6561–6568
135. Brown RT, Freeman WS, Perrin JM et al (2001) Prevalence and assessment of attention-deficit/hyperactivity disorder in primary care settings. *Pediatrics* 107:E43
136. Cuffe SP, Moore CG, McKeown RE (2005) Prevalence and correlates of ADHD symptoms in the national health interview survey. *J Atten Disord* 9:392–401. doi:[10.1177/1087054705280413](https://doi.org/10.1177/1087054705280413)
137. Smalley SL, McGough JJ, Moilanen IK et al (2007) Prevalence and psychiatric comorbidity of attention-deficit/hyperactivity disorder in an adolescent Finnish population. *J Am Acad Child Adolesc Psychiatry* 46:1575–1583. doi:[10.1097/chi.0b013e3181573137](https://doi.org/10.1097/chi.0b013e3181573137)
138. Gullledge AT, Bucci DJ, Zhang SS et al (2009) M1 receptors mediate cholinergic modulation of excitability in neocortical pyramidal neurons. *J Neurosci* 29:9888–9902. doi:[10.1523/JNEUROSCI.1366-09.2009](https://doi.org/10.1523/JNEUROSCI.1366-09.2009)
139. Lambe EK, Picciotto MR, Aghajanian GK (2003) Nicotine induces glutamate release from thalamocortical terminals in prefrontal cortex. *Neuropsychopharmacol* 28:216–225. doi:[10.1038/sj.npp.1300032](https://doi.org/10.1038/sj.npp.1300032)
140. Gioanni Y, Rougeot C, Clarke PB et al (1999) Nicotinic receptors in the rat prefrontal cortex: increase in glutamate release and facilitation of mediodorsal thalamo-cortical transmission. *Eur J Neurosci* 11:18–30
141. Lambe EK, Olausson P, Horst NK et al (2005) Hypocretin and nicotine excite the same thalamocortical synapses in prefrontal cortex: correlation with improved attention in rat. *J Neurosci* 25:5225–5229. doi:[10.1523/JNEUROSCI.0719-05.2005](https://doi.org/10.1523/JNEUROSCI.0719-05.2005)
142. Parikh V, Ji J, Decker MW, Sarter M (2010) Prefrontal beta2 subunit-containing and alpha7 nicotinic acetylcholine receptors differentially control glutamatergic and cholinergic signaling. *J Neurosci* 30:3518–3530. doi:[10.1523/JNEUROSCI.5712-09.2010](https://doi.org/10.1523/JNEUROSCI.5712-09.2010)
143. Livingstone PD, Dickinson JA, Srinivasan J et al (2010) Glutamate-dopamine crosstalk in the rat prefrontal cortex



- is modulated by Alpha7 nicotinic receptors and potentiated by PNU-120596. *J Mol Neurosci* 40:172–176. doi:[10.1007/s12031-009-9232-5](https://doi.org/10.1007/s12031-009-9232-5)
144. Livingstone PD, Srinivasan J, Kew JNC et al (2009) alpha7 and non-alpha7 nicotinic acetylcholine receptors modulate dopamine release in vitro and in vivo in the rat prefrontal cortex. *Eur J Neurosci* 29:539–550. doi:[10.1111/j.1460-9568.2009.06613.x](https://doi.org/10.1111/j.1460-9568.2009.06613.x)
  145. Kennett A, Heal DJ, Wonnacott S (2012) Pharmacological differences between rat frontal cortex and hippocampus in the nicotinic modulation of noradrenaline release implicate distinct receptor subtypes. *Nicotine Tob Res* 14:1339–1345. doi:[10.1093/ntr/nts128](https://doi.org/10.1093/ntr/nts128)
  146. Porter JT, Cauli B, Tsuzuki K et al (1999) Selective excitation of subtypes of neocortical interneurons by nicotinic receptors. *J Neurosci* 19:5228–5235
  147. Krenz I, Kalkan D, Wevers A et al (2001) Parvalbumin-containing interneurons of the human cerebral cortex express nicotinic acetylcholine receptor proteins. *J Chem Neuroanat* 21:239–246
  148. Alkondon M, Pereira EF, Eisenberg HM, Albuquerque EX (2000) Nicotinic receptor activation in human cerebral cortical interneurons: a mechanism for inhibition and disinhibition of neuronal networks. *J Neurosci* 20:66–75
  149. Couey JJ, Meredith RM, Spijker S et al (2007) Distributed network actions by nicotine increase the threshold for spike-timing-dependent plasticity in prefrontal cortex. *Neuron* 54:73–87. doi:[10.1016/j.neuron.2007.03.006](https://doi.org/10.1016/j.neuron.2007.03.006)
  150. Xiang Z, Huguenard JR, Prince DA (1998) Cholinergic switching within neocortical inhibitory networks. *Science* 281:985–988
  151. Vidal C, Changeux J-P (1993) Nicotinic and muscarinic modulations of excitatory synaptic transmission in the rat prefrontal cortex in vitro. *Neuroscience* 56:23–32
  152. Gil Z, Connors BW, Amitai Y (1997) Differential regulation of neocortical synapses by neuromodulators and activity. *Neuron* 19:679–686
  153. Christophe E, Roebuck A, Staiger JF et al (2002) Two types of nicotinic receptors mediate an excitation of neocortical layer I interneurons. *J Neurophysiol* 88:1318–1327. doi:[10.1152/jn.0199.2002](https://doi.org/10.1152/jn.0199.2002)
  154. Bandyopadhyay S (2006) Endogenous acetylcholine enhances synchronized interneuron activity in rat neocortex. *J Neurophysiol* 95:1908–1916. doi:[10.1152/jn.00881.2005](https://doi.org/10.1152/jn.00881.2005)
  155. Meyer-Lindenberg A, Weinberger DR (2006) Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nat Rev Neurosci* 7:818–827. doi:[10.1038/nrn1993](https://doi.org/10.1038/nrn1993)
  156. Tekin S, Cummings JL (2002) Frontal-subcortical neuronal circuits and clinical neuropsychiatry: an update. *J Psychosom Res* 53:647–654
  157. Nelson CL, Sarter M, Bruno JP (2005) Prefrontal cortical modulation of acetylcholine release in posterior parietal cortex. *Neuroscience* 132:347–359. doi:[10.1016/j.neuroscience.2004.12.007](https://doi.org/10.1016/j.neuroscience.2004.12.007)
  158. Arnsten AFT, Wang MJ, Paspalas CD (2012) Neuromodulation of thought: flexibilities and vulnerabilities in prefrontal cortical network synapses. *Neuron* 76:223–239. doi:[10.1016/j.neuron.2012.08.038](https://doi.org/10.1016/j.neuron.2012.08.038)
  159. Uylings HBM, Groenewegen HJ, Kolb B (2003) Do rats have a prefrontal cortex? *Behav Brain Res* 146:3–17
  160. Gaykema RPA, Luiten PGM, Nyakas C, Traber JR (1990) Cortical projection patterns of the medial septum-diagonal band complex. *J Comp Neurol* 293:103–124. doi:[10.1002/cne.902930109](https://doi.org/10.1002/cne.902930109)
  161. Zaborszky L, Gaykema RP, Swanson DJ, Cullinan WE (1997) Cortical input to the basal forebrain. *Neuroscience* 79:1051–1078
  162. Kumari V, Gray JA, Ffytche DH et al (2003) Cognitive effects of nicotine in humans: an fMRI study. *NeuroImage* 19:1002–1013. doi:[10.1016/S1053-8119\(03\)00110-1](https://doi.org/10.1016/S1053-8119(03)00110-1)
  163. Milham MP, Erickson KI, Banich MT et al (2002) Attentional control in the aging brain: insights from an fMRI Study of the Stroop Task. *Brain Cogn* 49:277–296. doi:[10.1006/brcg.2001.1501](https://doi.org/10.1006/brcg.2001.1501)
  164. Hao J, Li K, Li K et al (2005) Visual attention deficits in Alzheimer's disease: an fMRI study. *Neurosci Lett* 385:18–23. doi:[10.1016/j.neulet.2005.05.028](https://doi.org/10.1016/j.neulet.2005.05.028)
  165. Small DM, Gitelman DR, Gregory MD et al (2003) The posterior cingulate and medial prefrontal cortex mediate the anticipatory allocation of spatial attention. *NeuroImage* 18:633–641. doi:[10.1016/S1053-8119\(02\)00012-5](https://doi.org/10.1016/S1053-8119(02)00012-5)
  166. Hoyle E, Genn RF, Fernandes C, Stolerman IP (2006) Impaired performance of alpha7 nicotinic receptor knockout mice in the five-choice serial reaction time task. *Psychopharmacology* 189:211–223. doi:[10.1007/s00213-006-0549-2](https://doi.org/10.1007/s00213-006-0549-2)
  167. Young JW, Crawford N, Kelly JS et al (2007) Impaired attention is central to the cognitive deficits observed in alpha7 deficient mice. *Eur Neuropsychopharmacol* 17:145–155. doi:[10.1016/j.euroneuro.2006.03.008](https://doi.org/10.1016/j.euroneuro.2006.03.008)
  168. Rigbi A, Kanyas K, Yakir A et al (2008) Why do young women smoke? V. Role of direct and interactive effects of nicotinic cholinergic receptor gene variation on neurocognitive function. *Genes Brain Behav* 7:164–172. doi:[10.1111/j.1601-183X.2007.00329.x](https://doi.org/10.1111/j.1601-183X.2007.00329.x)
  169. Bierut LJ, Stitzel JA, Wang JC et al (2008) Variants in nicotinic receptors and risk for nicotine dependence. *Am J Psychiatry* 165:1163–1171. doi:[10.1176/appi.ajp.2008.07111711](https://doi.org/10.1176/appi.ajp.2008.07111711)
  170. Schlaepfer IR, Hoft NR, Collins AC et al (2008) The CHRNA5/A3/B4 gene cluster variability as an important determinant of early alcohol and tobacco initiation in young adults. *Biol Psychiatry* 63:1039–1046. doi:[10.1016/j.biopsych.2007.10.024](https://doi.org/10.1016/j.biopsych.2007.10.024)
  171. Stevens VL, Bierut LJ, Talbot JT et al (2008) Nicotinic receptor gene variants influence susceptibility to heavy smoking. *Cancer Epidemiol Biomarkers Prev* 17:3517–3525. doi:[10.1158/1055-9965.EPI-08-0585](https://doi.org/10.1158/1055-9965.EPI-08-0585)
  172. Weiss RB, Baker TB, Cannon DS et al (2008) A candidate gene approach identifies the CHRNA5-A3-B4 region as a risk factor for age-dependent nicotine addiction. *PLoS Genet* 4:e1000125. doi:[10.1371/journal.pgen.1000125](https://doi.org/10.1371/journal.pgen.1000125)
  173. Caporaso N, Gu F, Chatterjee N et al (2009) Genome-wide and candidate gene association study of cigarette smoking behaviors. *PLoS ONE* 4:e4653. doi:[10.1371/journal.pone.0004653](https://doi.org/10.1371/journal.pone.0004653)
  174. Saccone NL, Saccone SF, Hinrichs AL et al (2009) Multiple distinct risk loci for nicotine dependence identified by dense coverage of the complete family of nicotinic receptor subunit (CHRN) genes. *Am J Med Genet* 150B:453–466. doi:[10.1002/ajmg.b.30828](https://doi.org/10.1002/ajmg.b.30828)
  175. Prendergast MA, Jackson WJ, Terry AV et al (1998) Central nicotinic receptor agonists ABT-418, ABT-089, and (–)-nicotine reduce distractibility in adult monkeys. *Psychopharmacology* 136:50–58
  176. McGaughy J, Decker MW, Sarter M (1999) Enhancement of sustained attention performance by the nicotinic acetylcholine receptor agonist ABT-418 in intact but not basal forebrain-lesioned rats. *Psychopharmacology* 144:175–182
  177. Mirza NR, Bright JL (2001) Nicotine-induced enhancements in the five-choice serial reaction time task in rats are strain-dependent. *Psychopharmacology* 154:8–12. doi:[10.1007/s002130000605](https://doi.org/10.1007/s002130000605)
  178. Rezvani A, Bushnell P, Levin E (2002) Effects of nicotine and mecamylamine on choice accuracy in an operant visual signal detection task in female rats. *Psychopharmacology* 164:369–375. doi:[10.1007/s00213-002-1221-0](https://doi.org/10.1007/s00213-002-1221-0)

179. Rezvani AH, Cauley M, Sexton H et al (2011) Sazetidine-A, a selective  $\alpha 4\beta 2$  nicotinic acetylcholine receptor ligand: effects on dizocilpine and scopolamine-induced attentional impairments in female Sprague–Dawley rats. *Psychopharmacology* 215:621–630. doi:[10.1007/s00213-010-2161-8](https://doi.org/10.1007/s00213-010-2161-8)
180. Hahn B, Sharples CGV, Wonnacott S et al (2003) Attentional effects of nicotinic agonists in rats. *Neuropharmacology* 44:1054–1067. doi:[10.1016/S0028-3908\(03\)00099-6](https://doi.org/10.1016/S0028-3908(03)00099-6)
181. Grottick AJ, Higgins GA (2000) Effect of subtype selective nicotinic compounds on attention as assessed by the five-choice serial reaction time task. *Behav Brain Res* 117:197–208. doi:[10.1016/S0166-4328\(00\)00305-3](https://doi.org/10.1016/S0166-4328(00)00305-3)
182. Hahn B, Stolerman IP (2002) Nicotine-induced attentional enhancement in rats: effects of chronic exposure to nicotine. *Neuropsychopharmacol* 27:712–722. doi:[10.1016/S0893-133X\(02\)00348-2](https://doi.org/10.1016/S0893-133X(02)00348-2)
183. Pattij T, Janssen MCW, Loos M et al (2007) Strain specificity and cholinergic modulation of visuospatial attention in three inbred mouse strains. *Genes Brain Behav* 6:579–587. doi:[10.1111/j.1601-183X.2006.00284.x](https://doi.org/10.1111/j.1601-183X.2006.00284.x)
184. Picciotto MR (2003) Nicotine as a modulator of behavior: beyond the inverted U. *Trends Pharmacol Sci* 24:493–499. doi:[10.1016/S0165-6147\(03\)00230-X](https://doi.org/10.1016/S0165-6147(03)00230-X)
185. Newhouse PA, Potter A, Singh A (2004) Effects of nicotinic stimulation on cognitive performance. *Curr Opin Pharmacol* 4:36–46. doi:[10.1016/j.coph.2003.11.001](https://doi.org/10.1016/j.coph.2003.11.001)
186. Wesnes K, Warburton DM (1984) Effects of scopolamine and nicotine on human rapid information processing performance. *Psychopharmacology* 82:147–150
187. Mumenthaler MS, Taylor JL, O'Hara R, Yesavage JA (1998) Influence of nicotine on simulator flight performance in non-smokers. *Psychopharmacology* 140:38–41
188. Levin ED, Connors CK, Silva D et al (1998) Transdermal nicotine effects on attention. *Psychopharmacology* 140:135–141
189. Le Houezec J, Halliday R, Benowitz NL et al (1994) A low dose of subcutaneous nicotine improves information processing in non-smokers. *Psychopharmacology* 114:628–634
190. Kleykamp BA, Jennings JM, Blank MD, Eissenberg T (2005) The effects of nicotine on attention and working memory in never-smokers. *Psychol Addict Behav* 19:433–438. doi:[10.1037/0893-164X.19.4.433](https://doi.org/10.1037/0893-164X.19.4.433)
191. Heishman SJ, Snyder FR, Henningfield JE (1993) Performance, subjective, and physiological effects of nicotine in non-smokers. *Drug Alcohol Depend* 34:11–18
192. Foulds J, Stapleton J, Swettenham J et al (1996) Cognitive performance effects of subcutaneous nicotine in smokers and never-smokers. *Psychopharmacology* 127:31–38
193. Heishman SJ, Henningfield JE (2000) Tolerance to repeated nicotine administration on performance, subjective, and physiological responses in nonsmokers. *Psychopharmacology* 152:321–333. doi:[10.1007/s002130000541](https://doi.org/10.1007/s002130000541)
194. Parrott AC, Roberts G (1991) Smoking deprivation and cigarette reinstatement: effects upon visual attention. *J Psychopharmacol (Oxford)* 5:404–409. doi:[10.1177/026988119100500435](https://doi.org/10.1177/026988119100500435)
195. Warburton DM, Arnall C (1994) Improvements in performance without nicotine withdrawal. *Psychopharmacology* 115:539–542
196. Dawkins L, Powell JH, West R et al (2007) A double-blind placebo-controlled experimental study of nicotine: II—effects on response inhibition and executive functioning. *Psychopharmacology* 190:457–467. doi:[10.1007/s00213-006-0634-6](https://doi.org/10.1007/s00213-006-0634-6)
197. Newhouse PA, Sunderland T, Tariot PN et al (1988) Intravenous nicotine in Alzheimer's disease: a pilot study. *Psychopharmacology* 95:171–175
198. Zabala A, Eguiluz JI, Segarra R et al (2009) Cognitive performance and cigarette smoking in first-episode psychosis. *Eur Arch Psychiatry Clin Neurosci* 259:65–71. doi:[10.1007/s00406-008-0835-6](https://doi.org/10.1007/s00406-008-0835-6)
199. Henningfield JE, Stapleton JM, Benowitz NL et al (1993) Higher levels of nicotine in arterial than in venous blood after cigarette smoking. *Drug Alcohol Depend* 33:23–29
200. Rose JE, Mukhin AG, Lokitz SJ et al (2010) Kinetics of brain nicotine accumulation in dependent and nondependent smokers assessed with PET and cigarettes containing 11C-nicotine. *PNAS* 107:5190–5195. doi:[10.1073/pnas.0909184107](https://doi.org/10.1073/pnas.0909184107)
201. Matta SG, Balfour DJ, Benowitz NL et al (2007) Guidelines on nicotine dose selection for in vivo research. *Psychopharmacology* 190:269–319. doi:[10.1007/s00213-006-0441-0](https://doi.org/10.1007/s00213-006-0441-0)
202. Woollorton JRA, Pidoplichko VI, Broide RS, Dani JA (2003) Differential desensitization and distribution of nicotinic acetylcholine receptor subtypes in midbrain dopamine areas. *J Neurosci* 23:3176–3185
203. Gazzaley A, Cooney JW, Rissman J, D'Esposito M (2005) Top-down suppression deficit underlies working memory impairment in normal aging. *Nat Neurosci* 8:1298–1300. doi:[10.1038/nm1543](https://doi.org/10.1038/nm1543)
204. Cullum CM, Harris JG, Waldo MC et al (1993) Neurophysiological and neuropsychological evidence for attentional dysfunction in schizophrenia. *Schizophr Res* 10:131–141
205. Perry RJ, Hodges JR (1999) Attention and executive deficits in Alzheimer's disease. A critical review. *Brain* 122(Pt 3):383–404. doi:[10.1093/brain/122.3.383](https://doi.org/10.1093/brain/122.3.383)
206. Chen WJ, Faraone SV (2000) Sustained attention deficits as markers of genetic susceptibility to schizophrenia. *Am J Med Genet* 97:52–57
207. Gur RE, Calkins ME, Gur RC et al (2006) The consortium on the genetics of schizophrenia: neurocognitive endophenotypes. *Schizophr Bull* 33:49–68. doi:[10.1093/schbul/sbl055](https://doi.org/10.1093/schbul/sbl055)
208. Terrière E, Dempsey MF, Herrmann LL et al (2010) 5-123I-A-85380 binding to the  $\alpha 4\beta 2$ -nicotinic receptor in mild cognitive impairment. *Neurobiol Aging* 31:1885–1893. doi:[10.1016/j.neurobiolaging.2008.10.008](https://doi.org/10.1016/j.neurobiolaging.2008.10.008)
209. Kendziorra K, Wolf H, Meyer PM et al (2010) Decreased cerebral  $\alpha 4\beta 2^*$  nicotinic acetylcholine receptor availability in patients with mild cognitive impairment and Alzheimer's disease assessed with positron emission tomography. *Eur J Nucl Med Mol Imaging* 38:515–525. doi:[10.1007/s00259-010-1644-5](https://doi.org/10.1007/s00259-010-1644-5)
210. Wu J, Ishikawa M, Zhang J, Hashimoto K (2010) Brain imaging of nicotinic receptors in Alzheimer's disease. *Int J Alzheimer's Dis* 2010:1–11. doi:[10.1016/j.brainres.2010.08.095](https://doi.org/10.1016/j.brainres.2010.08.095)
211. Whitehouse PJ, Martino AM, Antuono PG et al (1986) Nicotinic acetylcholine binding sites in Alzheimer's disease. *Brain Res* 371:146–151
212. Nordberg A, Winblad B (1986) Reduced number of [3H]nicotine and [3H]acetylcholine binding sites in the frontal cortex of Alzheimer brains. *Neurosci Lett* 72:115–119
213. Nordberg A, Adem A, Hardy J, Winblad B (1988) Change in nicotinic receptor subtypes in temporal cortex of Alzheimer brains. *Neurosci Lett* 86:317–321
214. Sugaya K, Giacobini E, Chiappinelli VA (1990) Nicotinic acetylcholine receptor subtypes in human frontal cortex: changes in Alzheimer's disease. *J Neurosci Res* 27:349–359. doi:[10.1002/jnr.490270314](https://doi.org/10.1002/jnr.490270314)
215. Sihver W, Gillberg PG, Svensson AL, Nordberg A (1999) Autoradiographic comparison of [3H](-)-nicotine, [3H]cytisine and [3H]epibatidine binding in relation to vesicular acetylcholine transport sites in the temporal cortex in Alzheimer's disease. *Neuroscience* 94:685–696
216. Freedman R, Coon H, Myles-Worsley M et al (1997) Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *PNAS* 94:587–592

217. Guan ZZ, Zhang X, Blennow K, Nordberg A (1999) Decreased protein level of nicotinic receptor  $\alpha 7$  subunit in the frontal cortex from schizophrenic brain. *NeuroReport* 10:1779–1782
218. Hong LE, Yang X, Wonodi I et al (2011) A CHRNA5 allele related to nicotine addiction and schizophrenia. *Genes Brain Behav* 10:530–535. doi:10.1111/j.1601-183X.2011.00689.x
219. Jackson KJ, Fanous AH, Chen J et al (2013) Variants in the 15q25 gene cluster are associated with risk for schizophrenia and bipolar disorder. *Psychiatr Genet* 23:20–28. doi:10.1097/YPG.0b013e32835bd5f1
220. Martin L, Kem W, Freedman R (2004) Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. *Psychopharmacology*. doi:10.1007/s00213-003-1750-1
221. Kem WR (1997) Alzheimer's drug design based upon an invertebrate toxin (anabaseine) which is a potent nicotinic receptor agonist. *Invert Neurosci* 3:251–259
222. Kem WR, Mahnir VM, Prokai L et al (2004) Hydroxy metabolites of the Alzheimer's drug candidate 3-[(2,4-dimethoxy)benzylidene]-anabaseine dihydrochloride (GTS-21): their molecular properties, interactions with brain nicotinic receptors, and brain penetration. *Mol Pharmacol* 65:56–67. doi:10.1124/mol.65.1.56
223. Toyohara J, Hashimoto K (2010)  $\alpha 7$  Nicotinic receptor agonists: potential therapeutic drugs for treatment of cognitive impairments in schizophrenia and Alzheimer's disease. *Open Med Chem J* 4:37–56. doi:10.2174/1874104501004010037
224. Nie H, Wang Z, Zhao W et al (2013) Neuroscience letters. *Neurosci Lett* 537:29–34. doi:10.1016/j.neulet.2013.01.001
225. Wilens TE, Biederman J, Spencer TJ et al (1999) A pilot controlled clinical trial of ABT-418, a cholinergic agonist, in the treatment of adults with attention deficit hyperactivity disorder. *Am J Psychiatry* 156:1931–1937
226. Wilens TE, Gault LM, Childress A et al (2011) Safety and efficacy of ABT-089 in pediatric attention-deficit/hyperactivity disorder: results from two randomized placebo-controlled clinical trials. *J Am Acad Child Adolesc Psychiatry* 50(73–84):e1. doi:10.1016/j.jaac.2010.10.001
227. Apostol G, Abi-Saab W, Kratochvil CJ et al (2011) Efficacy and safety of the novel  $\alpha 4\beta 2$  neuronal nicotinic receptor partial agonist ABT-089 in adults with attention-deficit/hyperactivity disorder: a randomized, double-blind, placebo-controlled crossover study. *Psychopharmacology* 219:715–725. doi:10.1007/s00213-011-2393-2
228. Bain EE, Robieson W, Pritchett Y et al (2013) A randomized, double-blind, placebo-controlled phase 2 study of  $\alpha 4\beta 2$  agonist ABT-894 in adults with ADHD. *Neuropsychopharmacol* 38:405–413. doi:10.1038/npp.2012.194
229. Jucaite A, Öhd J, Potter AS et al (2013) A randomized, double-blind, placebo-controlled crossover study of  $\alpha 4\beta 2^*$  nicotinic acetylcholine receptor agonist AZD1446 (TC-6683) in adults with attention-deficit/hyperactivity disorder. *Psychopharmacology*. doi:10.1007/s00213-013-3116-7
230. Lester HA, Xiao C, Srinivasan R et al (2009) Nicotine is a selective pharmacological chaperone of acetylcholine receptor number and stoichiometry. Implications for drug discovery. *AAPS J* 11:167–177. doi:10.1208/s12248-009-9090-7
231. Miwa JM, Lester HA, Walz A (2012) Optimizing cholinergic tone through lynx modulators of nicotinic receptors: implications for plasticity and nicotine addiction. *Physiology* 27:187–99
232. Lewis AS, Picciotto MR (2013) High-affinity nicotinic acetylcholine receptor expression and trafficking abnormalities in psychiatric illness. *Psychopharmacology* 229:477–485. doi:10.1007/s00213-013-3126-5
233. Taly A, Corringier P-J, Guedin D et al (2009) Nicotinic receptors: allosteric transitions and therapeutic targets in the nervous system. *Nat Rev Drug Discov* 8:733–750. doi:10.1038/nrd2927
234. Young JW, Finlayson K, Spratt C et al (2004) Nicotine improves sustained attention in mice: evidence for involvement of the  $\alpha 7$  nicotinic acetylcholine receptor. *Neuropsychopharmacol* 29:891–900. doi:10.1038/sj.npp.1300393
235. Winterer G, Mittelstrass K, Giegling I et al (2010) Risk gene variants for nicotine dependence in the CHRNA5-CHRNA3-CHRNA4 cluster are associated with cognitive performance. *Am J Med Genet B Neuropsychiatr Genet* 153B:1448–1458. doi:10.1002/ajmg.b.31126
236. Todd RD, Lobos EA, Sun L-W, Neuman RJ (2003) Mutational analysis of the nicotinic acetylcholine receptor  $\alpha 4$  subunit gene in attention deficit/hyperactivity disorder: evidence for association of an intronic polymorphism with attention problems. *Molecular Psychiatry* 8:103–108. doi:10.1038/sj.mp.4001257
237. Greenwood PM, Fossella JA, Parasuraman R (2005) Specificity of the effect of a nicotinic receptor polymorphism on individual differences in visuospatial attention. *J Cognitive Neurosci* 17:1611–1620. doi:10.1162/089989905774597281
238. Espeseth T, Sneve MH, Rootwelt H, Laeng B (2010) Nicotinic receptor gene CHRNA4 interacts with processing load in attention. *PLoS ONE* 5:e14407. doi:10.1371/journal.pone.0014407
239. Muir JL, Everitt BJ, Robbins TW (1994) AMPA-induced excitotoxic lesions of the basal forebrain: a significant role for the cortical cholinergic system in attentional function. *J Neurosci* 14:2313–2326
240. Muir JL, Everitt BJ, Robbins TW (1995) Reversal of visual attentional dysfunction following lesions of the cholinergic basal forebrain by physostigmine and nicotine but not by the 5-HT3 receptor antagonist, ondansetron. *Psychopharmacology* 118:82–92
241. Muir JL, Everitt BJ, Robbins TW (1996) 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* 6:470–481
242. Chudasama Y, Passetti F, Rhodes SEV et al (2003) Dissociable aspects of performance on the 5-choice serial reaction time task following lesions of the dorsal anterior cingulate, infralimbic and orbitofrontal cortex in the rat: differential effects on selectivity, impulsivity and compulsivity. *Behav Brain Res* 146:105–119
243. Birrell JM, Brown VJ (2000) Medial frontal cortex mediates perceptual attentional set shifting in the rat. *J Neurosci* 20:4320–4324
244. Witte EA, Davidson MC, Marrocco RT (1997) Effects of altering brain cholinergic activity on covert orienting of attention: comparison of monkey and human performance. *Psychopharmacology* 132:324–334
245. Mirza NR, Stolerman IP (1998) Nicotine enhances sustained attention in the rat under specific task conditions. *Psychopharmacology* 138:266–274
246. Blondel A, Sanger DJ, Moser PC (2000) Characterisation of the effects of nicotine in the five-choice serial reaction time task in rats: antagonist studies. *Psychopharmacology* 149:293–305
247. Grilly DM, Simon BB, Levin ED (2000) Nicotine enhances stimulus detection performance of middle- and old-aged rats: a longitudinal study. *Pharmacol Biochem Behav* 65:665–670
248. Rezvani AH, Levin ED (2004) Nicotine-antipsychotic drug interactions and attentional performance in female rats. *Eur J Pharmacol* 486:175–182. doi:10.1016/j.ejphar.2003.12.021
249. Rezvani AH, Caldwell DP, Levin ED (2005) Nicotinic-serotonergic drug interactions and attentional performance in rats. *Psychopharmacology* 179:521–528. doi:10.1007/s00213-004-2060-y
250. Grottick AJ, Wyler R, Higgins GA (2001) A study of the nicotinic agonist SIB-1553A on locomotion and attention as

- measured by the five-choice serial reaction time task. *Pharmacol Biochem Behav* 70:505–513
251. Hahn B, Shoaib M, Stolerman IP (2002) Nicotine-induced enhancement of attention in the five-choice serial reaction time task: the influence of task demands. *Psychopharmacology* 162:129–137. doi:10.1007/s00213-002-1005-6
  252. Day M, Pan JB, Buckley MJ et al (2007) Differential effects of ciproxifan and nicotine on impulsivity and attention measures in the 5-choice serial reaction time test. *Biochem Pharmacol* 73:1123–1134. doi:10.1016/j.bcp.2006.12.004
  253. Hahn B, Shoaib M, Stolerman IP (2011) Selective nicotinic receptor antagonists: effects on attention and nicotine-induced attentional enhancement. *Psychopharmacology* 217:75–82. doi:10.1007/s00213-011-2258-8
  254. Semenova S, Stolerman IP, Markou A (2007) Chronic nicotine administration improves attention while nicotine withdrawal induces performance deficits in the 5-choice serial reaction time task in rats. *Pharmacol Biochem Behav* 87:360–368. doi:10.1016/j.pbb.2007.05.009
  255. Allison C, Shoaib M (2013) Nicotine improves performance in an attentional set shifting task in rats. *Neuropharmacology* 64:314–320. doi:10.1016/j.neuropharm.2012.06.055
  256. Young JW, Meves JM, Geyer MA (2013) Nicotinic agonist-induced improvement of vigilance in mice in the 5-choice continuous performance test. *Behav Brain Res* 240:119–133. doi:10.1016/j.bbr.2012.11.028
  257. Min S, Moon I-W, Ko R, Shin H (2001) Effects of transdermal nicotine on attention and memory in healthy elderly non-smokers. *Psychopharmacology* 159:83–88. doi:10.1007/s002130100899
  258. Griesar WS, Zajdel DP, Oken BS (2002) Nicotine effects on alertness and spatial attention in non-smokers. *Nicotine Tob Res* 4:185–194. doi:10.1080/14622200210123617
  259. Thiel CM, Zilles K, Fink GR (2005) Nicotine modulates reorienting of visuospatial attention and neural activity in human parietal cortex. *Neuropsychopharmacol*. doi:10.1038/sj.npp.1300633
  260. Giessing C, Thiel CM, Rösler F, Fink GR (2006) The modulatory effects of nicotine on parietal cortex activity in a cued target detection task depend on cue reliability. *Neuroscience* 137:853–864. doi:10.1016/j.neuroscience.2005.10.005
  261. Poltavski DV, Petros T (2006) Effects of transdermal nicotine on attention in adult non-smokers with and without attentional deficits. *Physiol Behav* 87:614–624. doi:10.1016/j.physbeh.2005.12.011
  262. Meinke A, Thiel CM, Fink GR (2006) Effects of nicotine on visuo-spatial selective attention as indexed by event-related potentials. *Neuroscience* 141:201–212. doi:10.1016/j.neuroscience.2006.03.072
  263. Vossel S, Thiel CM, Fink GR (2007) Behavioral and neural effects of nicotine on visuospatial attentional reorienting in non-smoking subjects. *Neuropsychopharmacol* 33:731–738. doi:10.1038/sj.npp.1301469
  264. Knott VJ, Bolton K, Heenan A et al (2009) Effects of acute nicotine on event-related potential and performance indices of auditory distraction in nonsmokers. *Nicotine Tob Res* 11:519–530. doi:10.1093/ntr/ntp044
  265. Knott VJ, Millar AM, McIntosh JF et al (2011) Separate and combined effects of low dose ketamine and nicotine on behavioural and neural correlates of sustained attention. *Biol Psychol* 88:83–93. doi:10.1016/j.biopsycho.2011.06.012
  266. Wignall ND, de Wit H (2011) Effects of nicotine on attention and inhibitory control in healthy nonsmokers. *Exp Clin Psychopharmacol* 19:183–191. doi:10.1037/a0023292
  267. Myers CS, Taylor RC, Salmeron BJ et al (2013) Nicotine enhances alerting, but not executive, attention in smokers and nonsmokers. *Nicotine Tob Res* 15:277–281. doi:10.1093/ntr/nts108
  268. Terry AV, Risbrough VB, Buccafusco JJ, Menzaghi F (2002) Effects of ( $\pm$ )-4-[[2-(1-methyl-2-pyrrolidinyl)ethyl]thio]phenol hydrochloride (SIB-1553A), a selective ligand for nicotinic acetylcholine receptors, in tests of visual attention and distractibility in rats and monkeys. *J Pharmacol Exp Ther* 301:284–292
  269. Buccafusco JJ, Terry AV Jr, Decker MW, Gopalakrishnan M (2007) Profile of nicotinic acetylcholine receptor agonists ABT-594 and A-582941, with differential subtype selectivity, on delayed matching accuracy by young monkeys. *Biochem Pharmacol* 74:1202–1211. doi:10.1016/j.bcp.2007.07.010
  270. Rezvani AH, Kholdebarin E, Brucato FH et al (2009) Effect of R3487/MEM3454, a novel nicotinic  $\alpha$ 7 receptor partial agonist and 5-HT3 antagonist on sustained attention in rats. *Progress Neuropsychopharmacol Biol Psychiatry* 33:269–275. doi:10.1016/j.pnpbp.2008.11.018
  271. Mohler EG, Franklin SR, Rueter LE et al (2010) Pharmacology, biochemistry and behavior. *Pharmacol Biochem Behav* 95:146–157. doi:10.1016/j.pbb.2009.12.019
  272. Mirza NR, Stolerman IP (2000) The role of nicotinic and muscarinic acetylcholine receptors in attention. *Psychopharmacology* 148:243–250
  273. Ruotsalainen S, Miettinen R, MacDonald E et al (2000) Blockade of muscarinic, rather than nicotinic, receptors impairs attention, but does not interact with serotonin depletion. *Psychopharmacology* 148:111–123
  274. Ellis JR, Ellis KA, Bartholomeusz CF et al (2006) Muscarinic and nicotinic receptors synergistically modulate working memory and attention in humans. *Int J Neuropsychopharmacol* 9:175–189. doi:10.1017/S1461145705005407
  275. Yesavage JA, Mumenthaler MS, Taylor JL et al (2002) Donepezil and flight simulator performance: effects on retention of complex skills. *Neurology* 59:123–125
  276. Rokem A, Landau AN, Garg D et al (2010) Cholinergic enhancement increases the effects of voluntary attention but does not affect involuntary attention. *Neuropsychopharmacol* 35:2538–2544. doi:10.1038/npp.2010.118
  277. Paxinos G, Franklin K (2001) The mouse brain in stereotaxic coordinates, 2nd edn. Academic Press, San Diego
  278. Luiten PG, Gaykema RP, Traber J, Spencer DG (1987) Cortical projection patterns of magnocellular basal nucleus subdivisions as revealed by anterogradely transported *Phaseolus vulgaris* leucoagglutinin. *Brain Res* 413:229–250
  279. McKay BE, Placzek AN, Dani JA (2007) Regulation of synaptic transmission and plasticity by neuronal nicotinic acetylcholine receptors. *Biochem Pharmacol* 74:1120–1133. doi:10.1016/j.bcp.2007.07.001
  280. Dalley JW, Cardinal RN, Robbins TW (2004) Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. *Neurosci Biobehav Rev* 28:771–784. doi:10.1016/j.neubiorev.2004.09.006
  281. Bailey CDC, Tian MK, Kang L, O'Reilly R, Lambe EK (2013) ChRNA5 genotype determines the long-lasting effects of developmental in vivo nicotine exposure on prefrontal attention circuitry. *Neuropharmacology*. doi:10.1016/j.neuropharm.2013.09.003