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Research Update for **Special Issue** 'Nicotinic Receptor-based Therapeutics'

Nicotinic actions on neuronal networks for cognition: General principles and long-term consequences

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Abstract

Nicotine enhances cognitive performance in humans and laboratory animals. The immediate positive actions of nicotine on learning, memory and attention are well-documented. Several brain areas involved in cognition, such as the prefrontal cortex, have been implicated. Besides acute effects on these brain areas and on brain function, a picture is emerging showing that long-term consequences of nicotine exposure during adolescence can be detrimental for cognitive performance. The majority of adult smokers started the habit during adolescence. Our knowledge on the types of nicotinic receptors in the brain areas that are candidates for mediating nicotine's effects is increasing. However, much less is known about the underlying cellular mechanisms. A series of recent studies have uncovered exciting features of the mechanisms by which nicotine alters prefrontal cortex neuronal activity, synaptic plasticity, gene expression and cognitive function, and how these changes may have a lasting effect on the developing brain. In this review, we discuss these exciting findings and identify several common principles by which nicotinic receptor activation modulates cortical circuits involved in cognition. Understanding how nicotine induces long-term changes in neuronal circuits and alters plasticity in the prefrontal cortex is essential to determining how these mechanisms interact to alter cognition.

Key words: Acetylcholine, Nicotine, Prefrontal cortex, Neuronal networks, Synaptic plasticity, Development

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Nicotine and cognitive function

It has long been recognized that nicotine, the addictive substance in cigarettes, can have stimulating effects on brain function. The link to the psychoactive effects lies in the fact that nicotine stimulates nicotinic acetylcholine receptors (nAChRs) that are normally activated by the endogenous neurotransmitter acetylcholine (ACh) and interfere with cholinergic signalling. By boosting signal-to-noise ratio, the cholinergic system in the brain is important for a variety of cognitive functions, such as learning, memory and attention processes that involve many different brain regions [1]. Specifically in prefrontal cortex (PFC) cholinergic signals are involved in attention [2]. The entire cortex is innervated by projections from the basal forebrain that release ACh [1]. Nicotinic AChRs, with their highly dense and widespread distribution in neocortical and subcortical areas [3], are an important component of the ACh system. It comes therefore as no surprise that nicotine can affect cognitive processes both in humans and rodents [4-7].

The strong involvement of cholingergic signalling in cognitive functions was shown in studies where selective depletion of ACh in target areas or lesions of ACh projections was applied (reviewed in [2]. In tests that asses attention behaviour, which strongly relies on prefrontal cortex function, selective lesions in the basal forebrain cholinergic system as well as depletion of ACh directly in PFC result in a reduction in attention performance [8-10]. These data agree with studies showing a positive correlation between cortical acetylcholine release and attentional demand [11]. Attention deficits induced by lesions can be ameliorated by pharmacological agents that augment cholinergic signalling in the PFC [12]. In view of these findings, it is not surprising that activation of nAChRs can affect cognitive functions and, in particular, attentional performance. With a few exceptions, nAChRs agonists enhance cognitive

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performance, while antagonists have the adverse effect [7] . For instance, nicotinic agonists improve working memory function [13] and overcome deficits induced by lesioning cholinergic innervation of the hippocampus [14, 15]. In contrast, nicotinic antagonists for different nicotinic subtypes applied to the hippocampus impair working memory function in the radial arm maze [16]. Some aspects of this enhancement appear to rely particularly on nicotinic receptor signalling in the prefrontal cortex [17]. Also in humans, nicotine was shown to enhance activity in the prefrontal cortex [18]. Finally, the enhancement of attention performance by nicotinic agonists was shown in a number of studies [7, 12, 17, 19-22].

Very little is known about the mechanisms underlying nicotine's power as cognitive enhancer. Even less is known about the long-term consequences of nicotine exposure for cognitive performance. Our understanding of how nicotinic compounds affect cortical circuits involved in cognition is far from complete, but in this review recently uncovered important new insights in these mechanisms will be highlighted.

Nicotinic receptors

Nicotinic AChRs belong to the cys-loop ligand-gated ion-channel family [23]. This group of pentameric transmembrane proteins form a water-filled pore upon binding of neurotransmitter after which charged ions can flow over the membrane. Twelve genes have been identified encoding neuronal nicotinic receptors [for review see 24]. Each gene encodes a subunit of the receptor that can be classified into α-type subunits and non-α-type subunits, based on the presence or absence, respectively, of a pair of cysteine amino acids [23-25, reviewed in 26, 27-29]. This cysteine pair is important for agonist binding and it has been thought therefore that α-subunits at least in part regulate agonist binding. In the central nervous system 9 α -subunits (α2–α10

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encoded by CHRNA2–10) and 3 β-type subunits (β2–β4; CHRNB2–4) are expressed. These subunits assemble in different stoichiometries to form the pentameric channel, and the subunit composition of nAChRs varies depending on the brain region [for review see 23, 24, 30, 31-34]. Nicotinic receptors can either assemble as homomeric or heteromeric channels. Heteromeric channels are formed by a combination between α and β subunits, whereas some α subunits can assemble into a homomeric channel. When opened, the nicotinic receptor is a cation selective channel which permits flow of Na^+, K^+ and Ca^{2+} across the membrane. At normal resting membrane potential this leads to a depolarizing current. The impact of nAChR activation on neuronal function strongly depends on the subunit composition of the nAChRs. Each subunit combination has its own activation and desensitization characteristics and has different single channel conductance and agonist selectivity, potentially leading to different kinetics of depolarizing currents in the target cell [15, 23].

The two most abundant nicotinic receptors in the brain are receptors that contain α4β2 or α7 subunits. α4β2* receptors have a very high affinity for nicotine and desensitize at low concentrations of nicotine, corresponding to blood concentrations experienced by smokers [23, 35]. In contrast, the homomeric channels containing α7 subunits have a low affinity for nicotine but do not desensitize at low nicotinic concentrations [36, 37]. These phenomena will have significant impact on how these receptors are activated in neuronal networks (see below). Another distinctive feature of these receptors is their permeability for calcium. Amino acids lining the pore of the protein largely determine the ion-selectivity of the channel. α7* nicotinic receptors are highly permeable for calcium compared to α4β2* receptors [38]. They serve, therefore, a distinguished role because this calcium influx can influence cellular processes like neurotransmitter release and synaptic plasticity

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directly. It has been suggested that α7* nicotinic receptors perform a complementary role to NMDA receptors. These channels are also calcium permeable, but are only opened at a more depolarized membrane potential [39].

Nicotinic AChRs in the PFC

There is ample evidence that nAChR activation in general affects attention performance [4, 7, 40, 41], but much less is known about the nAChR subtypes and brain areas involved. Several studies point to a specific role of cholinergic signalling in the medial prefrontal cortex and attention performance [9, 17]. However, only a limited number of studies have addressed the role of nAChR subtypes in the PFC and their role in attention behavior. Infusion of α-bungarotoxin, an α7* nicotinic receptor antagonist, into the prefrontal cortex impairs performance in a delayed response task, which requires effortful processing for response selection [42]. β2-containing nAChRs have also been implicated in mediating effects of nicotine on attention performance. Nicotine decreased response latency and reduced incorrect responses in the 5-choice serial reaction time task [43], a test that assesses sustained attention performance [44]. These effects of nicotine were completely antagonized by dihydro-β-erythroidine (DHβE), a specific blocker for β2-containing nicotinic receptors. In this study, methyllycaconitine (MLA), a somewhat selective blocker of α7-containing nAChRs, did not alter the effects of nicotine [43]. However, genetic approaches assessing the role of nAChRs have shown that α7* receptors do have a role in attention. Knockout mice lacking the gene for the α7 nAChR subunits showed impaired task acquisition and a higher rate of omissions in the 5-choice serial reaction time task [45, 46]. Since the mice used for these studies lacked α7* nAChR expression throughout their brains, it is not known whether the impairment in

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attention performance was attributable to the lack of α7* receptors specifically in the PFC, let alone whether the effects were attributable to a specific type of cells in the PFC neuronal circuits. If nicotinic compounds are to be designed as cognitive enhancers for therapeutic use, a detailed understanding of how nAChR activation affects PFC microcircuits will be indispensible.

Nicotine's modes of action

The large body of evidence demonstrating that nAChRs can affect cognitive processes offers an enticing chance to link protein function to complex behaviour [4, 5, 7, 47]. However, to understand the mechanisms involved at the level of neuronal networks, there are several bridges yet to be built. Typically, a cortical microcircuit consists of a set of excitatory and inhibitory neurons that are interconnected using highly dynamic connections. To understand how nAChR activation in the prefrontal cortex affects cognitive behaviour, an understanding is needed of how prefrontal cortical microcircuits generate output from the inputs they receive. One of the challenges is to distinguish the cell types and the connectivity patterns that are present in the prefrontal cortex circuitry. The next step is to understand how nicotine alters the functionality of these neuronal circuits. General principles on how nicotine affects microcircuits in the brain will depend on (i) which cell types in the circuits express nicotinic receptors and (ii) from which subunits these receptors are made of. The latter strongly determines activation and desensitization kinetics, agonist sensitivity and ion-specific channel conductance. (iii) The sub-cellular location of the receptor will determine what stage of information processing is affected, since nicotinic receptors can be found on dendritic, somatic, axonal and presynaptic compartments. Nicotinic AChRs expressed in axons or axon terminals can alter release of neurotransmitter at

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specific sites, even independent of action potential depolarization [48-52]. This often results in an increased probability of release at these sites, changing how the information carried by these synapses enters and is processed by the cortex. Alternatively, nicotinic AChRs can alter whole neuron functions by changing resting membrane potentials. These nicotinic currents can drastically alter the availability of Na and K channels available for action potential generation (through inactivation), affect resting membrane potential (depolarization), and even potentially alter regional voltage signals via shunting [36, 53-55].

(iv) Given the fact that nAChR can be continuously activated by endogenous ACh, nAChR desensitization can affect ongoing neuronal activity just as nAChR activation [36, 37, 56, 57]. Therefore, the dynamics of endogenous cholinergic signalling will play an important role in the effects of exogenously administered nicotinic compounds. The dynamics of cholinergic signalling in the cortex during ongoing behaviour has long remained enigmatic. Due to low temporal resolution of classical techniques such as microdialysis, cholinergic modulation was considered to occur on a timescale of minutes [11, 58]. However, recently it was shown that cholinergic signalling involved in attention has a much faster temporal dynamics, suggesting that cholinergic signals convey more information than just arousing a network into an 'excited' state [2, 59]. How the interplay between nAChR activation and deactivation on a subsecond time scale by endogenous ACh and exogenously applied agonists will affect cortical neuronal network activity remains to be elucidated.

(v) Finally, it will be of significance whether nAChRs are activated by direct synaptic contact or via a slower process like volume transmission. Spill over and

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diffusion of ACh will result in different activation and desensitization profiles compared to targeted fast synaptic release.

These factors will combine to alter neuronal network properties and will be central to understanding nicotine's effects on higher cognitive functions. Although we are only beginning to understand how nicotine is affecting neuronal circuits in the prefrontal cortex, several features have now been uncovered, some of which show similarities to cholinergic modulation of other cortical areas, emphasizing that common principles may exist guiding nicotinic modulation of cortical circuits.

Nicotinic modulation of thalamocortical communication

One of the first recognized functions for nAChRs in the central nervous system was its role in enhancing neurotransmitter release [48]. As first described in chicken medial habenula-interpeduncular synapses and later in the mossy fiber synapse in the rat hippocampus, nicotine augments synaptic release of glutamate via presynaptic receptors [48, 60]. The facilitating effect of nicotine was dependent on the extracellular calcium concentration, and nicotine application leads to a higher calcium signal in mossy fiber boutons. Depending on the subunit composition and precise location, nicotinic receptors can enhance presynaptic neurotransmitter release either through depolarization or direct calcium influx or both [61].

Nicotinic AChRs on axonal projections play a key role in regulating the transmission of thalamic information to the cortex [50, 52, 62-64]. Transdermal administration of nicotine to non-smokers does not affect cochlear activity but does affect the neural transmission of acoustic information [65]. A similar result was observed in the rat auditory cortex [66]. Critically, in this study antagonists of nAChRs reduced the evoked signal in the cortex, suggesting that endogenous ACh

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acts through nAChRs to regulate thalamic transmission. The barrel cortex of the rat is perhaps the best studied model of thalamocortical transmission, and here too nicotinic agonists can alter cortical processing. Topical application of nicotinic agonist to the exposed cortex in-vivo increased the size of a whisker's functional representation in the cortex [67]. Earlier recordings in thalamocortical slices from the barrel cortex support this result by demonstrating that thalamic synapses, unlike intracortical synapses, are modulated by nAChRs [68]. Even in the visual cortex, nicotine can increase responsiveness to visual stimuli [18, 69].

Although the prefrontal cortex is thought to be a higher order processing area, it receives thalamic input from the dorsal medial nucleus of the thalamus. Thalamocortical glutamatergic transmission to the prefrontal cortex is augmented by the activation of nAChRs [52, 55, 63, 70, 71]. Autoradiographic labelling of nAChRs was reduced after lesions in the medial dorsal thalamus (MDT). This suggested that nAChRs are present on thalamocortical terminals and could potentially alter thalamic information processing in the PFC. When neurons in the MDT are stimulated *in vivo* action potentials are elicited in the prefrontal cortex. Infusing nicotine locally into the PFC enhanced the response elicited in the prefrontal cortex. Microdialysis experiments showed that nicotine induced glutamate release in the PFC which could be blocked by DHβE [63]. Lesioning the MDT strongly reduced the augmentation of glutamatergic inputs to layer V pyramidal neurons by nicotine [52]. This suggests that among the glutamatergic inputs received by layer V pyramidal neurons, nicotine selectively stimulates thalamic inputs (Figure 1). As with thalamocortical inputs to somatosensory cortex, the nAChRs responsible for the augmentation by nicotine were located away from the presynaptic terminal, most likely on the axons themselves [50, 52]. These nicotinic mechanisms differ from the mechanisms by which nicotine

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increases excitatory transmission in the hippocampus and VTA, where activation of α7* receptors leads to a direct stimulation of glutamate release [51, 60]. Support for modulatory effects of presynaptic nAChRs activation in the PFC comes from a variety of approaches including electrophysiological recordings and assay of release from isolated nerve terminals [72-74]. A recent study testing the relative contribution of β2*nAChRs vs. α7*nAChRs on glutamatergic synaptosomes from PFC [72] demonstrated that both α7* and non α7*nAChRs appear to be important although each modulates excitatory amino acid (EAA) release via distinct mechanisms. Taken together, these data suggest that nicotine selectively increases activity of inputs from the thalamus to the cortex over other glutamatergic synapses.

Understanding how nAChRs can affect the function of cortical pyramidal neurons is essential to understanding nicotine's effects on cognition. However, the task is significantly more complicated. While so many aspects of pyramidal cell function are well described, nAChRs are rarely found on pyramidal cells in the cortex [55, 75]. A recent study has found nAChRs on layer VI pyramidal cells [71] (Figure 1). This specific population represents pyramidal cells projecting back to the thalamus. Despite the fact that nAChRs are rarely found on pyramidal cells, nicotine can still affect their function in many ways. In addition to glutamatergic inputs to layer V pyramidal neurons, glutamatergic inputs to several types of layer V interneurons were also excited by nicotine with a similar pharmacological profile [55]. Although it was not shown in the study, it is tempting to speculate that these nicotine-sensitive glutamatergic inputs to interneurons were of thalamic origin, but this waits further testing. Nicotinic regulation of excitatory inputs to inhibitory interneurons could serve to balance excitation and inhibition in the prefrontal cortex,

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which is thought to be crucial for cortical functioning and information processing [76].

Cortical interneurons and nicotinic actions

Inhibitory neurons of the neocortex comprise a comparatively more diverse population of cells than excitatory cells. At least two types of interneurons are recognized to be morphologically and functionally distinct classes: fast spiking cells (FS) and low-threshold spiking cells (LTS) [76-81]. Fast spiking cells (FS) are physiologically equipped for high frequency firing, show little adaptation, and have been shown to synapse on or near the somata of their target cells [81-84]. As such, they occupy an ideal functional and morphological position to regulate the input window of pyramidal cells [85]. At least one study in the somatosensory cortex has demonstrated this functional position for FS cells [86]. Their functional role also appears to extend to regulating plasticity in this microcircuit [87]. This association with thalamic inputs has also been confirmed in the PFC [88]. While there is some disagreement as to whether this FS cells express nAChRs, this discrepancy appears to be species specific. Studies in rodents have failed to find nAChRs on FS cells in the cortex [55, 75] (Figure 1). In contrast, in at least one study FS cells in human cortex appear to express nAChRs [89]. FS cells appear to be important in regulating the precise timing of information coming into the cortex, and there is emerging consensus evidence that LTS interneurons play a role in shaping feedforward inhibition between excitatory cells [90, 91]. Like FS cells, LTS cells target specific dendritic subdomains of their target pyramids. In contrast to FS cells which are thought to regulate target cell activation and activity, LTS cells appear to regulate specific inputs to pyramidal cell apical dendrites, as well as mediating interlaminar feedforward inhibition in the

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cortex. These interneurons express large nicotinic currents, and excitatory input to these cells is also enhanced by nicotine [55, 75, 92]. A third class of interneurons, identified based on their firing properties in response to depolarizing current steps, regular-spiking non-pyramidal neurons, were also excited by nicotine [55] (Figure 1).

Nicotinic AChR activation and synaptic plasticity

Synaptic plasticity is critically important for cognitive function, and in particular, synaptic plasticity in the PFC has been directly associated with attention and working memory [93]. The relative timing of action potentials in pre- and postsynaptic neurons has a profound impact on the induction of long-term potentiation or depression. When a presynaptic spike precedes a postsynaptic spike within a short time window of several tens of milliseconds, LTP is induced. The reverse order of spike-timing results in long term depression (LTD) [94, 95]. In mouse PFC, nicotine strongly affects this timing-dependent synaptic plasticity, which is called spike-timing-dependent plasticity (STDP). Stimulation of nicotinic AChRs in PFC modifies STDP induced by pairing stimulation of the excitatory inputs to PFC layer 5 pyramidal neurons with postsynaptic spikes elicited 5 ms after each synaptic response [55]. This coordinated stimulation induced robust LTP; however, when the same stimulus paradigm was applied in the presence of nicotine concentrations experienced by smokers, LTP was eliminated and a depression of the excitatory inputs to these cells was observed. Which nAChRs on what neurons are responsible for this effect? As discussed above, mouse PFC layer 5 pyramidal neurons do not express nicotinic receptors themselves. Rather, the nAChRs involved in the nicotinic modulation of LTP induction increase inhibitory GABAergic inputs to the pyramidal cells, as the nicotinic modulation of plasticity was abolished by inhibitors of GABA type A

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($GABA_A$) receptors. As described above, LTS and RSNP GABAergic interneurons found in the PFC layer 5 express nAChR subunits on their soma that activate these neurons when nicotine is present. FS interneurons are excited indirectly by nAChRs that increase glutamatergic excitation of those cells. Thus, nicotine exposure enhances inhibitory input to the layer V pyramidal neurons through both direct and indirect excitation of inhibitory GABA interneurons (Figure 1).

Studies in other cortical areas indicate that increases in postsynaptic calcium concentration are critical for the induction of synaptic plasticity [96-98]. Using two-photon imaging of intracellular calcium levels, it was found that action potentials that propagated from the soma into the dendrites of layer 5 pyramidal cells elicited increases in dendritic calcium concentration. Nicotine enhanced the GABA input to the same dendrites, resulting in less calcium entry, likely due to failure of action potential back-propagation from the soma. Thus, nicotine suppresses postsynaptic calcium changes, thereby altering the conditions necessary for synaptic potentiation. Burst-like stimulation of the pyramidal cell in the presence of nicotine could restore postsynaptic calcium to concentrations comparable to those seen in the absence of nicotine, as well as the STDP, indicating that strong postsynaptic stimulation could overcome the nicotinic modulation [55, 99].

The activation of distributed nAChRs provides the PFC neuronal network with a wide range of computational possibilities, but the functional consequences of this modulation are hard to predict from these data alone. Nicotine alters the rules for synaptic plasticity resulting from timed presynaptic and postsynaptic activity and increases LTP threshold by reducing dendritic calcium signals. As such, the function of the medial PFC network will most likely change in the presence of nicotine. Most likely, distal apical dendrite of layer 5 pyramidal neurons in superficial layers will be

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more quantitatively affected by the nicotinic mechanisms we found to block STDP than the synapses that are located closer to the cell body. By reducing dendritic action potential propagation in apical dendrites, nicotine hampers communication between cell body and distal synapses in layer 5 pyramidal neurons. This potentially could strongly affect information processing in the neuronal network of the medial PFC as a whole, and will alter the output of the PFC. At the same time, increased activity in pyramidal neurons restores the conditions for STDP to occur. The presence of nicotine and increased threshold for STDP could reduce cognitive performance in healthy naive rodents [100]. Alternatively, since PFC neuronal activity could be increased during PFC-based cognitive behavior, nicotine may provide conditions under which signal-to-noise ratio in PFC information processing is enhanced, thereby improving cognitive performance [41, 100]. It is possible that enhancing signal-to-noise for phasic activity within the PFC, rather than simply increasing excitability, could be an effective mechanism for cognition-enhancing drugs.

Through the mechanisms discussed above, nicotinic AChR activation directly affects activity in cortical circuits involved in cognition. However, these same cellular and synaptic mechanisms also affect long-term synaptic plasticity, the effects of which outlast nAChR activation [51, 55, 101]. Thereby, nicotine may exert lasting effects on cognition. Thus far, a very limited number of studies have addressed this hypothesis, and mechanisms underlying long-term effects of nAChR activation have not been addressed. The majority of adult smokers started the habit during adolescence [102, 103], and evidence is accumulating that the adolescent brain is vulnerable for precipitating lasting changes upon nicotine exposure. In the following

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sections, we will discuss the evidence for lasting effects of nAChR activation on cortical networks and cognitive function upon adolescent nicotine exposure.

Cortical development and nAChRs

Acetylcholine and nAChRs play critical roles in virtually all phases of brain maturation, during embryogenesis as well as postnatal development [reviewed in 104]. During postnatal development of sensory cortices there is a dramatic, transient increase in the expression of AChE [105]. Concurrently, nAChR ′Υ7 subunit gene expression also transiently increases in sensory cortices. Binding of [^{125}I]′ΥBgTx - to assess nAChR ′Υ7 levels - starts at birth in rat sensory cortex, peaks at postnatal day 10, and then declines to adult concentrations by postnatal day 20 [106]. Expression of ′Υ7 subunit mRNA follows a similar time course [107]. Moderate to high levels of messenger RNA are maintained into the first postnatal week, followed by a decline into adulthood [107]. The increase in cortical ′Υ7 mRNA precedes by the arrival of AChE-labeled thalamocortical afferents and preventing these afferents from reaching the cortex strongly reduces the ′Υ7 subunit mRNA and [^{125}I]′ΥBgTx binding in layers IV and VI [108], suggesting that the expression of ′Υ7 subunit-containing nAChRs is regulated by thalamic inputs. These ′Υ7 subunit-containing nAChRs could be located post-synaptically as well as pre-synaptically, on thalamic afferents. It has been hypothesized that pre-synaptic ′Υ7 nAChRs in primary auditory cortex are involved in the maturation of glutamate synapses by facilitating the conversion of 'silent synapses', containing only NMDA receptors into mature AMPA and NMDA receptor containing synapses [64, 109]. The authors suggest that through this mechanism of nAChR-induced maturation of glutamate synapses, the expression of ′Υ7 subunits in the auditory cortex could define a critical period of sensory cortex development in

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which synaptic refinement of cortical circuitry and tuning to sensory inputs takes place.

In developing hippocampus, nAChRs containing ′ϒ7 subunits can also activate 'silent' synapses that show a low probability of being active and turn them into high probability synapses [110]. Schaffer collateral to CA1 synapses that have a high probability of being active during development can be down-regulated by ′ϒ7 and ύ2 subunits-containing nAChRs [111]. In the rat PFC, there are strong developmental changes in nicotinic signalling of pyramidal neurons in layer VI. The nicotinic currents recorded from these neurons mediated by α5-containing nAChRs peak at postnatal week 3 [71]. In human brain, the levels of nAChRs also show region-specific changes in development. Towards birth nicotine receptor binding is at its highest density, then nAChR levels start declining with the rate dependent on brain area: there is an apparent rapid decline in the hippocampus, whereas in cortical areas nicotine binding falls more gradually [112]. These findings suggest that nicotinic receptors play a role during development of excitatory glutamatergic connections and can contribute to shaping cortical neuronal circuitry.

In humans, as well as in rodents and other mammals, brain development is far from complete at birth, and many neuronal systems mature in response to the continuous interaction with the changing environment. This is especially true for the areas of the brain involved in higher cognitive functions, such as PFC, that shows dynamic changes in grey and white matter proceeding late into adolescence[113, 114]. This delayed maturation of PFC involves on the cellular level active rewiring of the intrinsic circuitry, particularly pyramidal –pyramidal connections within PFC and the local inhibitory circuitry [115, 116]. Also PFC depending cognitive performance such

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as working memory and processing speed, voluntary response suppression, level off only by late adolescence [117-119].

Cholinergic signalling through nAChRs plays an important role in brain maturation. Similar to development of the PFC, the cholinergic system innervating it follows a more prolonged developmental time period [120]. When cholinergic innervation is disrupted during early postnatal development, delayed cortical neuronal development and permanent changes in cortical cytoarchitecture and cognitive behaviors are observed [121]. Thus, nAChRs appear to play multiple functional roles in brain development and their expression profiles coincide with important phases in cortical maturation. Since PFC maturation occurs later than other cortical areas and continues into late adolescence, the lasting effects of nicotine exposure on prefrontal cortex function may be especially strong during the adolescent period.

Long-term consequences of nicotine exposure during adolescence

An ever-growing amount of evidence shows that nicotine exposure during adolescence not only has direct effects on prefrontal cortical function but can also lead to adaptations in this brain area that last into adulthood. Adolescent smoking strongly correlates with cognitive and behavioural impairments during later life [122-124]. Functional MRI studies show that during working memory and attention tasks adolescent smokers have reduced PFC activation, less efficiency and altered functional coordination than in abstinent adolescents [125, 126]. Importantly, the history of smoking duration in years is correlated with the extent of diminished PFC activity, suggesting that nicotine exerts long-lasting effects on PFC function [126]. Though studies in humans reveal strong correlations between adolescent smoking and cognitive impairments during later life, genetic variability and diverse social

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environment make it almost impossible to disentangle the causal relationships. Animal models with a highly uniform genetic and environmental background between individuals offer the opportunity to directly address lasting prefrontal adaptations in response to nicotine exposure.

In rodents, nicotine exposure during adolescence induces stronger changes in gene expression in the PFC than during other periods of development and adulthood [127-129]. In PFC after chronic nicotine treatment, the maximal regulation of genes involved in vesicle release, signal transduction, cytoskeleton dynamics and transcription was observed at postnatal day 35, suggesting the role of nicotine in initiating long-term structural and functional adaptations in adolescent PFC [129]. The activity of specific early response genes (arc) was found to be elevated in adolescent PFC after acute nicotine exposure [127]. In addition, c-fos expression in the PFC in response to nicotine exposure is maximal during adolescence [102]. The expression of key molecules involved in plasticity is also altered in the PFC by adolescent nicotine exposure. Acute nicotine induces increases in the expression of the dendritically targeted dendrin mRNA in PFC of adolescent but not adult animals. Dendrin is an important component of cytoskeletal modifications at the synapse and therefore can lead to unique plasticity changes in the adolescent PFC [128]. Lasting synaptic adaptations involve activation of intracellular signalling pathway and such enzymes as extracellular regulated protein kinase (ERK) and cAMP response element binding protein (CREB). Specifically in the PFC, increases in phosphorylation of both these enzymes were found after repeated nicotine exposure [130]. Also changes in macromolecular constituents indicative of cell loss (reduced DNA) and altered cell size (protein/DNA ratio) can be seen in cortical regions of rodents after adolescent nicotine treatment [131].

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Though these results describe direct changes after nicotine exposure, altered expression of genes involved in neuroplasticity can lead to structural changes in PFC neurons that last into adulthood. And indeed, repeated nicotine exposure also changes the structure of neurons in medial PFC: it increases both dendritic length and spine density [132]. Long-term changes have been observed in dendritic morphology of specific subpopulations of pyramidal neurons and these structural changes depended on the age of drug exposure [133]. Adolescent nicotine pretreatment produced an increase in basilar dendritic length in complex but not simple cells, while after adult nicotine exposure similar effect was seen in simple cells but not in complex [133].

Thus nicotine induces significant changes in gene expression and neuronal morphology in PFC specifically during the adolescent period. The key question now is of course, does adolescent nicotine exposure result in lasting altered cognitive function? Recently, this question was addressed by Counotte et al. [134]. Rats were trained in the 5 choice serial reaction time task [44] and were injected with either nicotine or saline for 10 days during adolescence (postnatal days 34 – 43) and attention performance was tested 5 weeks after the animals received the last injection with nicotine. Animals that received nicotine during adolescence showed a doubling in premature responses and a reduction in correct responses, suggesting increased impulsive behaviour and reduced attention performance [134]. Animals that received nicotine as adults did not show changes in impulsivity nor in attention performance [134]. What the mechanisms are underlying these lasting effects of nicotine on cognitive performance is at this point unknown.

Conclusions

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Nicotine's effects on cognition imply a vital role for nAChRs in cortical function. While several studies point to nAChRs in the PFC as central to nicotine's effects on attention performance, general principles on nAChR regulation of thalamic inputs may apply to the neocortex. In general, the data thus far point to nicotinic actions on two different information streams: glutamatergic input from the thalamus to the neocortex is excited by β2 subunit-containing nAChRs that are located on axons, but most likely not on the presynaptic terminals [52]. Within the neocortex, GABAergic transmission is enhanced by nicotine. Most of these nicotinic receptors are of the β2* or α7* type and are located on the cell bodies of interneurons, or on the excitatory inputs to these interneurons [55]. Recently, important new features of nicotinic modulation of cortical circuits have been uncovered. Pyramidal neurons of layer VI contain α5 subunit-containing nAChRs that directly excite these neurons [71]. Despite these findings, large gaps remain in our understanding of nicotinic modulation of cortical circuits involved in cognition. For instance, little is known about the type of interneurons that are present in layer VI and how they are modulated by nicotine. PFC layers II and III are also still 'terra incognita' when it comes to nicotinic mechanisms. It will be exciting to learn whether in these layers common features can be identified that apply to other cortical areas.

From animal experiments, the long-term consequences of adolescent nicotine exposure for prefrontal function in adult life are emerging. Our understanding of the mechanisms is still fragmentary, but the field of research on the role of nicotinic signalling in neuronal network development and cognition function is opening up. Depending on the developmental stage, the magnitude of effects induced by nicotine and the specific targets affected by nicotine vary. In adolescence, when brain development is still ongoing, the PFC appears to be a vulnerable target for lasting

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nicotinic actions. In rodents, even a short exposure to nicotine during this period can induce a cascade of intracellular signalling, gene expression profiles and structural changes that last into adulthood and may induce permanent deficiencies in attention and cognitive control. The challenge that lies ahead is to uncover the exact mechanisms underlying these long-term consequences of nicotine-induced cognitive impairments.

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Figure Legend

Figure 1.

Schematic model of the prefrontal cortex microcircuit and the identified nAChR subunits found to be expressed by the different cell types. The assignment of nAChR subunits to cell types and projections is mainly based on references [52, 55, 71], but are in line with findings in other cortical areas [64]. P: pyramidal neuron; FS: Fast Spiking interneuron; LTS: Low threshold spiking interneuron; RSNP: Regular spiking non-pyramidal interneuron.

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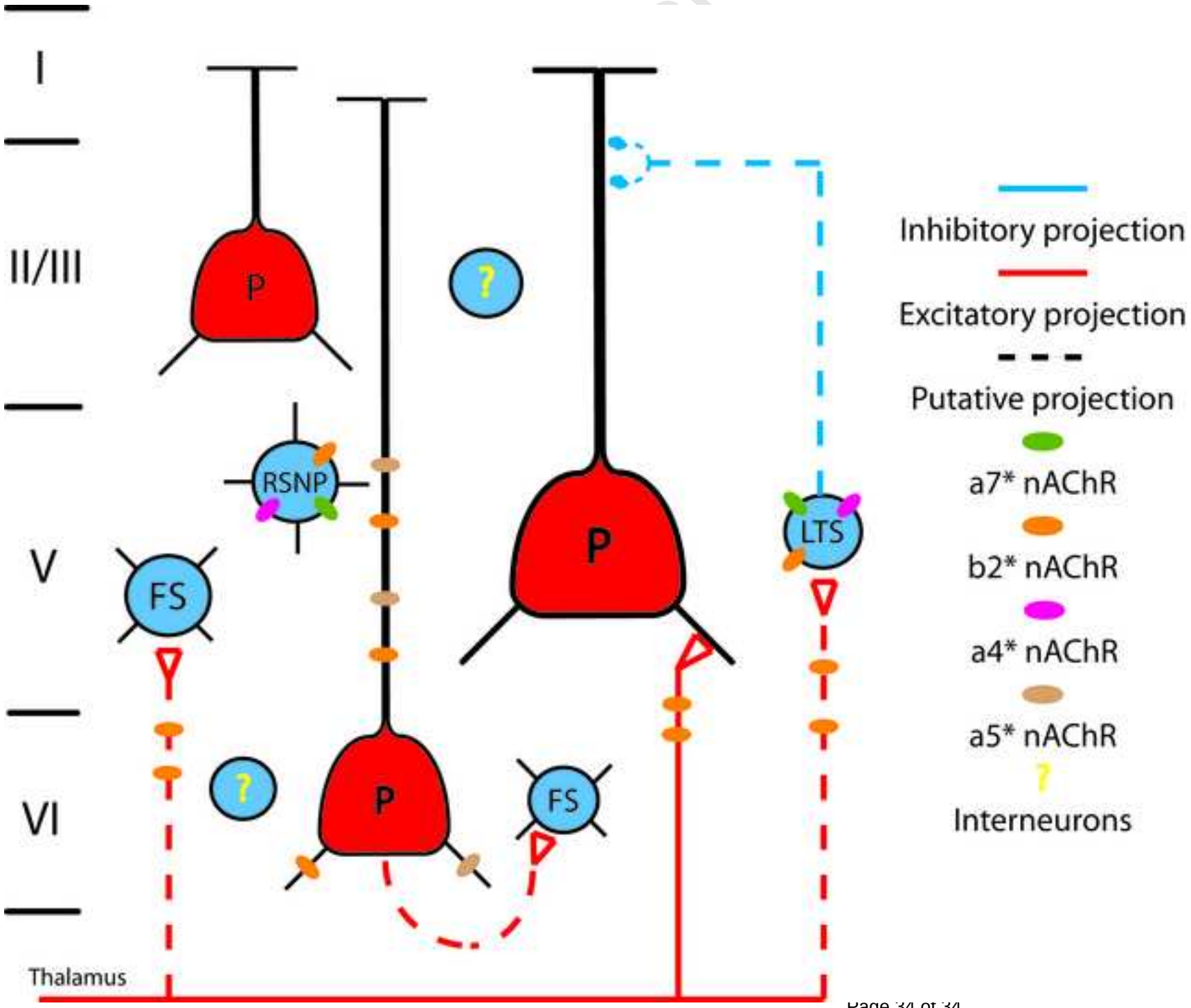
Figure


I
II/III
V
VI
P
?
RSNP
FS
P
LTS
?
P
FS
Thalamus
Inhibitory projection
Excitatory projection
Putative projection
a7* nAChR
b2* nAChR
a4* nAChR
a5* nAChR
Interneurons