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Research Update for **Special Issue** ‘Nicotinic Receptor-based Therapeutics’

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7 Nicotinic actions on neuronal networks for cognition:

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10 General principles and long-term consequences

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Running title: Nicotinic actions on neuronal networks for cognition

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Abstract

1
2 Nicotine enhances cognitive performance in humans and laboratory animals. The
3
4 immediate positive actions of nicotine on learning, memory and attention are well-
5
6 documented. Several brain areas involved in cognition, such as the prefrontal cortex,
7
8 have been implicated. Besides acute effects on these brain areas and on brain function,
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10 a picture is emerging showing that long-term consequences of nicotine exposure
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12 during adolescence can be detrimental for cognitive performance. The majority of
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14 adult smokers started the habit during adolescence. Our knowledge on the types of
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16 nicotinic receptors in the brain areas that are candidates for mediating nicotine's
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18 effects is increasing. However, much less is known about the underlying cellular
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20 mechanisms. A series of recent studies have uncovered exciting features of the
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22 mechanisms by which nicotine alters prefrontal cortex neuronal activity, synaptic
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24 plasticity, gene expression and cognitive function, and how these changes may have a
25
26 lasting effect on the developing brain. In this review, we discuss these exciting
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28 findings and identify several common principles by which nicotinic receptor
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30 activation modulates cortical circuits involved in cognition. Understanding how
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32 nicotine induces long-term changes in neuronal circuits and alters plasticity in the
33
34 prefrontal cortex is essential to determining how these mechanisms interact to alter
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36 cognition.
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Key words: Acetylcholine, Nicotine, Prefrontal cortex, Neuronal networks, Synaptic plasticity, Development

Nicotine and cognitive function

1
2 It has long been recognized that nicotine, the addictive substance in cigarettes,
3
4 can have stimulating effects on brain function. The link to the psychoactive effects
5
6 lies in the fact that nicotine stimulates nicotinic acetylcholine receptors (nAChRs) that
7
8 are normally activated by the endogenous neurotransmitter acetylcholine (ACh) and
9
10 interfere with cholinergic signalling. By boosting signal-to-noise ratio, the cholinergic
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12 system in the brain is important for a variety of cognitive functions, such as learning,
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14 memory and attention processes that involve many different brain regions [1].
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16 Specifically in prefrontal cortex (PFC) cholinergic signals are involved in attention
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18 [2]. The entire cortex is innervated by projections from the basal forebrain that release
19
20 ACh [1]. Nicotinic AChRs, with their highly dense and widespread distribution in
21
22 neocortical and subcortical areas [3], are an important component of the ACh system.
23
24 It comes therefore as no surprise that nicotine can affect cognitive processes both in
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26 humans and rodents [4-7].
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34 The strong involvement of cholinergic signalling in cognitive functions was
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36 shown in studies where selective depletion of ACh in target areas or lesions of ACh
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38 projections was applied (reviewed in [2]). In tests that assess attention behaviour, which
39
40 strongly relies on prefrontal cortex function, selective lesions in the basal forebrain
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42 cholinergic system as well as depletion of ACh directly in PFC result in a reduction in
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44 attention performance [8-10]. These data agree with studies showing a positive
45
46 correlation between cortical acetylcholine release and attentional demand [11].
47
48 Attention deficits induced by lesions can be ameliorated by pharmacological agents
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50 that augment cholinergic signalling in the PFC [12]. In view of these findings, it is not
51
52 surprising that activation of nAChRs can affect cognitive functions and, in particular,
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54 attentional performance. With a few exceptions, nAChRs agonists enhance cognitive
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1 performance, while antagonists have the adverse effect [7] . For instance, nicotinic
2 agonists improve working memory function [13] and overcome deficits induced by
3
4 lesioning cholinergic innervation of the hippocampus [14, 15]. In contrast, nicotinic
5
6 antagonists for different nicotinic subtypes applied to the hippocampus impair
7
8 working memory function in the radial arm maze [16]. Some aspects of this
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10 enhancement appear to rely particularly on nicotinic receptor signalling in the
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12 prefrontal cortex [17]. Also in humans, nicotine was shown to enhance activity in the
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14 prefrontal cortex [18]. Finally, the enhancement of attention performance by nicotinic
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16 agonists was shown in a number of studies [7, 12, 17, 19-22].
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22 Very little is known about the mechanisms underlying nicotine's power as
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24 cognitive enhancer. Even less is known about the long-term consequences of nicotine
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26 exposure for cognitive performance. Our understanding of how nicotinic compounds
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28 affect cortical circuits involved in cognition is far from complete, but in this review
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30 recently uncovered important new insights in these mechanisms will be highlighted.
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36 *Nicotinic receptors*

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38 Nicotinic AChRs belong to the cys-loop ligand-gated ion-channel family [23].
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40 This group of pentameric transmembrane proteins form a water-filled pore upon
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42 binding of neurotransmitter after which charged ions can flow over the membrane.
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44 Twelve genes have been identified encoding neuronal nicotinic receptors [for review
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46 see 24]. Each gene encodes a subunit of the receptor that can be classified into α -type
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48 subunits and non- α -type subunits, based on the presence or absence, respectively, of a
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50 pair of cysteine amino acids [23-25, reviewed in 26, 27-29]. This cysteine pair is
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52 important for agonist binding and it has been thought therefore that α -subunits at least
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54 in part regulate agonist binding. In the central nervous system 9 α -subunits ($\alpha 2$ - $\alpha 10$)
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1 encoded by CHRNA2–10) and 3 β -type subunits (β 2– β 4; CHRNB2–4) are expressed.
2 These subunits assemble in different stoichiometries to form the pentameric channel,
3 and the subunit composition of nAChRs varies depending on the brain region [for
4 review see 23, 24, 30, 31-34]. Nicotinic receptors can either assemble as homomeric
5 or heteromeric channels. Heteromeric channels are formed by a combination between
6 α and β subunits, whereas some α subunits can assemble into a homomeric channel.
7 When opened, the nicotinic receptor is a cation selective channel which permits flow
8 of Na^+ , K^+ and Ca^{2+} across the membrane. At normal resting membrane potential this
9 leads to a depolarizing current. The impact of nAChR activation on neuronal function
10 strongly depends on the subunit composition of the nAChRs. Each subunit
11 combination has its own activation and desensitization characteristics and has
12 different single channel conductance and agonist selectivity, potentially leading to
13 different kinetics of depolarizing currents in the target cell [15, 23].

14 The two most abundant nicotinic receptors in the brain are receptors that
15 contain α 4 β 2 or α 7 subunits. α 4 β 2* receptors have a very high affinity for nicotine
16 and desensitize at low concentrations of nicotine, corresponding to blood
17 concentrations experienced by smokers [23, 35]. In contrast, the homomeric channels
18 containing α 7 subunits have a low affinity for nicotine but do not desensitize at low
19 nicotinic concentrations [36, 37]. These phenomena will have significant impact on
20 how these receptors are activated in neuronal networks (see below). Another
21 distinctive feature of these receptors is their permeability for calcium. Amino acids
22 lining the pore of the protein largely determine the ion-selectivity of the channel. α 7*
23 nicotinic receptors are highly permeable for calcium compared to α 4 β 2* receptors
24 [38]. They serve, therefore, a distinguished role because this calcium influx can
25 influence cellular processes like neurotransmitter release and synaptic plasticity

1 directly. It has been suggested that $\alpha 7^*$ nicotinic receptors perform a complementary
2 role to NMDA receptors. These channels are also calcium permeable, but are only
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4 opened at a more depolarized membrane potential [39].
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9 *Nicotinic AChRs in the PFC*

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11 There is ample evidence that nAChR activation in general affects attention
12 performance [4, 7, 40, 41], but much less is known about the nAChR subtypes and
13
14 brain areas involved. Several studies point to a specific role of cholinergic signalling
15
16 in the medial prefrontal cortex and attention performance [9, 17]. However, only a
17
18 limited number of studies have addressed the role of nAChR subtypes in the PFC and
19
20 their role in attention behavior. Infusion of α -bungarotoxin, an $\alpha 7^*$ nicotinic receptor
21
22 antagonist, into the prefrontal cortex impairs performance in a delayed response task,
23
24 which requires effortful processing for response selection [42]. $\beta 2$ -containing
25
26 nAChRs have also been implicated in mediating effects of nicotine on attention
27
28 performance. Nicotine decreased response latency and reduced incorrect responses in
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30 the 5-choice serial reaction time task [43], a test that assesses sustained attention
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32 performance [44]. These effects of nicotine were completely antagonized by dihydro-
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34 β -erythroidine (DH β E), a specific blocker for $\beta 2$ -containing nicotinic receptors. In
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36 this study, methyllycaconitine (MLA), a somewhat selective blocker of $\alpha 7$ -containing
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38 nAChRs, did not alter the effects of nicotine [43]. However, genetic approaches
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40 assessing the role of nAChRs have shown that $\alpha 7^*$ receptors do have a role in
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42 attention. Knockout mice lacking the gene for the $\alpha 7$ nAChR subunits showed
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44 impaired task acquisition and a higher rate of omissions in the 5-choice serial reaction
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46 time task [45, 46]. Since the mice used for these studies lacked $\alpha 7^*$ nAChR
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48 expression throughout their brains, it is not known whether the impairment in
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1 attention performance was attributable to the lack of $\alpha 7^*$ receptors specifically in the
2 PFC, let alone whether the effects were attributable to a specific type of cells in the
3 PFC neuronal circuits. If nicotinic compounds are to be designed as cognitive
4 enhancers for therapeutic use, a detailed understanding of how nAChR activation
5 affects PFC microcircuits will be indispensable.
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14 *Nicotine's modes of action*

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16 The large body of evidence demonstrating that nAChRs can affect cognitive
17 processes offers an enticing chance to link protein function to complex behaviour [4,
18 5, 7, 47]. However, to understand the mechanisms involved at the level of neuronal
19 networks, there are several bridges yet to be built. Typically, a cortical microcircuit
20 consists of a set of excitatory and inhibitory neurons that are interconnected using
21 highly dynamic connections. To understand how nAChR activation in the prefrontal
22 cortex affects cognitive behaviour, an understanding is needed of how prefrontal
23 cortical microcircuits generate output from the inputs they receive. One of the
24 challenges is to distinguish the cell types and the connectivity patterns that are present
25 in the prefrontal cortex circuitry. The next step is to understand how nicotine alters the
26 functionality of these neuronal circuits. General principles on how nicotine affects
27 microcircuits in the brain will depend on (i) which cell types in the circuits express
28 nicotinic receptors and (ii) from which subunits these receptors are made of. The latter
29 strongly determines activation and desensitization kinetics, agonist sensitivity and
30 ion-specific channel conductance. (iii) The sub-cellular location of the receptor will
31 determine what stage of information processing is affected, since nicotinic receptors
32 can be found on dendritic, somatic, axonal and presynaptic compartments. Nicotinic
33 AChRs expressed in axons or axon terminals can alter release of neurotransmitter at
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1 specific sites, even independent of action potential depolarization [48-52]. This often
2 results in an increased probability of release at these sites, changing how the
3 information carried by these synapses enters and is processed by the cortex.
4 Alternatively, nicotinic AChRs can alter whole neuron functions by changing resting
5 membrane potentials. These nicotinic currents can drastically alter the availability of
6 Na and K channels available for action potential generation (through inactivation),
7 affect resting membrane potential (depolarization), and even potentially alter regional
8 voltage signals via shunting [36, 53-55].

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

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53 (v) Finally, it will be of significance whether nAChRs are activated by direct
54 synaptic contact or via a slower process like volume transmission. Spill over and
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1 diffusion of ACh will result in different activation and desensitization profiles
2 compared to targeted fast synaptic release.
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5 These factors will combine to alter neuronal network properties and will be
6
7 central to understanding nicotine's effects on higher cognitive functions. Although we
8
9 are only beginning to understand how nicotine is affecting neuronal circuits in the
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11 prefrontal cortex, several features have now been uncovered, some of which show
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13 similarities to cholinergic modulation of other cortical areas, emphasizing that
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15 common principles may exist guiding nicotinic modulation of cortical circuits.
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21 *Nicotinic modulation of thalamocortical communication*

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24 One of the first recognized functions for nAChRs in the central nervous
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26 system was its role in enhancing neurotransmitter release [48]. As first described in
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28 chicken medial habenula-interpeduncular synapses and later in the mossy fiber
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30 synapse in the rat hippocampus, nicotine augments synaptic release of glutamate via
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32 presynaptic receptors [48, 60]. The facilitating effect of nicotine was dependent on the
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34 extracellular calcium concentration, and nicotine application leads to a higher calcium
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36 signal in mossy fiber boutons. Depending on the subunit composition and precise
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38 location, nicotinic receptors can enhance presynaptic neurotransmitter release either
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40 through depolarization or direct calcium influx or both [61].
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47 Nicotinic AChRs on axonal projections play a key role in regulating the
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49 transmission of thalamic information to the cortex [50, 52, 62-64]. Transdermal
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51 administration of nicotine to non-smokers does not affect cochlear activity but does
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53 affect the neural transmission of acoustic information [65]. A similar result was
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55 observed in the rat auditory cortex [66]. Critically, in this study antagonists of
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57 nAChRs reduced the evoked signal in the cortex, suggesting that endogenous ACh
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1 acts through nAChRs to regulate thalamic transmission. The barrel cortex of the rat is
2 perhaps the best studied model of thalamocortical transmission, and here too nicotinic
3 agonists can alter cortical processing. Topical application of nicotinic agonist to the
4 exposed cortex in-vivo increased the size of a whisker's functional representation in
5 the cortex [67]. Earlier recordings in thalamocortical slices from the barrel cortex
6 support this result by demonstrating that thalamic synapses, unlike intracortical
7 synapses, are modulated by nAChRs [68]. Even in the visual cortex, nicotine can
8 increase responsiveness to visual stimuli [18, 69].

19 Although the prefrontal cortex is thought to be a higher order processing area,
20 it receives thalamic input from the dorsal medial nucleus of the thalamus.
21 Thalamocortical glutamatergic transmission to the prefrontal cortex is augmented by
22 the activation of nAChRs [52, 55, 63, 70, 71]. Autoradiographic labelling of nAChRs
23 was reduced after lesions in the medial dorsal thalamus (MDT). This suggested that
24 nAChRs are present on thalamocortical terminals and could potentially alter thalamic
25 information processing in the PFC. When neurons in the MDT are stimulated *in vivo*
26 action potentials are elicited in the prefrontal cortex. Infusing nicotine locally into the
27 PFC enhanced the response elicited in the prefrontal cortex. Microdialysis
28 experiments showed that nicotine induced glutamate release in the PFC which could
29 be blocked by DH β E [63]. Lesioning the MDT strongly reduced the augmentation of
30 glutamatergic inputs to layer V pyramidal neurons by nicotine [52]. This suggests that
31 among the glutamatergic inputs received by layer V pyramidal neurons, nicotine
32 selectively stimulates thalamic inputs (Figure 1). As with thalamocortical inputs to
33 somatosensory cortex, the nAChRs responsible for the augmentation by nicotine were
34 located away from the presynaptic terminal, most likely on the axons themselves [50,
35 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 $\alpha 7^*$ 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 $\beta 2^*$ nAChRs vs. $\alpha 7^*$ nAChRs on glutamatergic synaptosomes from PFC [72] demonstrated that both $\alpha 7^*$ and non $\alpha 7^*$ 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

1 cortex. These interneurons express large nicotinic currents, and excitatory input to
2 these cells is also enhanced by nicotine [55, 75, 92]. A third class of interneurons,
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4 identified based on their firing properties in response to depolarizing current steps,
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6 regular-spiking non-pyramidal neurons, were also excited by nicotine [55] (Figure 1).
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10 11 *Nicotinic AChR activation and synaptic plasticity*

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14 Synaptic plasticity is critically important for cognitive function, and in
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16 particular, synaptic plasticity in the PFC has been directly associated with attention
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18 and working memory [93]. The relative timing of action potentials in pre- and
19
20 postsynaptic neurons has a profound impact on the induction of long-term potentiation
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22 or depression. When a presynaptic spike precedes a postsynaptic spike within a short
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24 time window of several tens of milliseconds, LTP is induced. The reverse order of
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26 spike-timing results in long term depression (LTD) [94, 95]. In mouse PFC, nicotine
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28 strongly affects this timing-dependent synaptic plasticity, which is called spike-
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30 timing-dependent plasticity (STDP). Stimulation of nicotinic AChRs in PFC modifies
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32 STDP induced by pairing stimulation of the excitatory inputs to PFC layer 5
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34 pyramidal neurons with postsynaptic spikes elicited 5 ms after each synaptic response
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36 [55]. This coordinated stimulation induced robust LTP; however, when the same
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38 stimulus paradigm was applied in the presence of nicotine concentrations experienced
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40 by smokers, LTP was eliminated and a depression of the excitatory inputs to these
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42 cells was observed. Which nAChRs on what neurons are responsible for this effect?
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45 As discussed above, mouse PFC layer 5 pyramidal neurons do not express nicotinic
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47 receptors themselves. Rather, the nAChRs involved in the nicotinic modulation of
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49 LTP induction increase inhibitory GABAergic inputs to the pyramidal cells, as the
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51 nicotinic modulation of plasticity was abolished by inhibitors of GABA type A
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1 (GABA_A) receptors. As described above, LTS and RSNP GABAergic interneurons
2 found in the PFC layer 5 express nAChR subunits on their soma that activate these
3 neurons when nicotine is present. FS interneurons are excited indirectly by nAChRs
4 that increase glutamatergic excitation of those cells. Thus, nicotine exposure enhances
5 inhibitory input to the layer V pyramidal neurons through both direct and indirect
6 excitation of inhibitory GABA interneurons (Figure 1).
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14 Studies in other cortical areas indicate that increases in postsynaptic calcium
15 concentration are critical for the induction of synaptic plasticity [96-98]. Using two-
16 photon imaging of intracellular calcium levels, it was found that action potentials that
17 propagated from the soma into the dendrites of layer 5 pyramidal cells elicited
18 increases in dendritic calcium concentration. Nicotine enhanced the GABA input to
19 the same dendrites, resulting in less calcium entry, likely due to failure of action
20 potential back-propagation from the soma. Thus, nicotine suppresses postsynaptic
21 calcium changes, thereby altering the conditions necessary for synaptic potentiation.
22 Burst-like stimulation of the pyramidal cell in the presence of nicotine could restore
23 postsynaptic calcium to concentrations comparable to those seen in the absence of
24 nicotine, as well as the STDP, indicating that strong postsynaptic stimulation could
25 overcome the nicotinic modulation [55, 99].
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44 The activation of distributed nAChRs provides the PFC neuronal network with
45 a wide range of computational possibilities, but the functional consequences of this
46 modulation are hard to predict from these data alone. Nicotine alters the rules for
47 synaptic plasticity resulting from timed presynaptic and postsynaptic activity and
48 increases LTP threshold by reducing dendritic calcium signals. As such, the function
49 of the medial PFC network will most likely change in the presence of nicotine. Most
50 likely, distal apical dendrite of layer 5 pyramidal neurons in superficial layers will be
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1 more quantitatively affected by the nicotinic mechanisms we found to block STDP
2 than the synapses that are located closer to the cell body. By reducing dendritic action
3 potential propagation in apical dendrites, nicotine hampers communication between
4 cell body and distal synapses in layer 5 pyramidal neurons. This potentially could
5 strongly affect information processing in the neuronal network of the medial PFC as a
6 whole, and will alter the output of the PFC. At the same time, increased activity in
7 pyramidal neurons restores the conditions for STDP to occur. The presence of
8 nicotine and increased threshold for STDP could reduce cognitive performance in
9 healthy naive rodents [100]. Alternatively, since PFC neuronal activity could be
10 increased during PFC-based cognitive behavior, nicotine may provide conditions
11 under which signal-to-noise ratio in PFC information processing is enhanced, thereby
12 improving cognitive performance [41, 100]. It is possible that enhancing signal-to-
13 noise for phasic activity within the PFC, rather than simply increasing excitability,
14 could be an effective mechanism for cognition-enhancing drugs.

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

1 sections, we will discuss the evidence for lasting effects of nAChR activation on
2 cortical networks and cognitive function upon adolescent nicotine exposure.
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6 7 *Cortical development and nAChRs* 8

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10 Acetylcholine and nAChRs play critical roles in virtually all phases of brain
11 maturation, during embryogenesis as well as postnatal development [reviewed in
12 104]. During postnatal development of sensory cortices there is a dramatic, transient
13 increase in the expression of AChE [105]. Concurrently, nAChR $\gamma 7$ subunit gene
14 expression also transiently increases in sensory cortices. Binding of [125 I] γ BgTx - to
15 assess nAChR $\gamma 7$ levels - starts at birth in rat sensory cortex, peaks at postnatal day
16 10, and then declines to adult concentrations by postnatal day 20 [106]. Expression of
17 $\gamma 7$ subunit mRNA follows a similar time course [107]. Moderate to high levels of
18 messenger RNA are maintained into the first postnatal week, followed by a decline
19 into adulthood [107]. The increase in cortical $\gamma 7$ mRNA precedes by the arrival of
20 AChE-labeled thalamocortical afferents and preventing these afferents from reaching
21 the cortex strongly reduces the $\gamma 7$ subunit mRNA and [125 I] γ BgTx binding in layers
22 IV and VI [108], suggesting that the expression of $\gamma 7$ subunit-containing nAChRs is
23 regulated by thalamic inputs. These $\gamma 7$ subunit-containing nAChRs could be located
24 post-synaptically as well as pre-synaptically, on thalamic afferents. It has been
25 hypothesized that pre-synaptic $\gamma 7$ nAChRs in primary auditory cortex are involved in
26 the maturation of glutamate synapses by facilitating the conversion of 'silent
27 synapses', containing only NMDA receptors into mature AMPA and NMDA receptor
28 containing synapses [64, 109]. The authors suggest that through this mechanism of
29 nAChR-induced maturation of glutamate synapses, the expression of $\gamma 7$ subunits in
30 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 $\gamma 7$ 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 $\gamma 7$ and $\delta 2$ 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 $\alpha 5$ -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

1 as working memory and processing speed, voluntary response suppression, level off
2 only by late adolescence [117-119].
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4 Cholinergic signalling through nAChRs plays an important role in brain
5 maturation. Similar to development of the PFC, the cholinergic system innervating it
6 follows a more prolonged developmental time period [120]. When cholinergic
7 innervation is disrupted during early postnatal development, delayed cortical neuronal
8 development and permanent changes in cortical cytoarchitecture and cognitive
9 behaviors are observed [121]. Thus, nAChRs appear to play multiple functional roles
10 in brain development and their expression profiles coincide with important phases in
11 cortical maturation. Since PFC maturation occurs later than other cortical areas and
12 continues into late adolescence, the lasting effects of nicotine exposure on prefrontal
13 cortex function may be especially strong during the adolescent period.
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31 *Long-term consequences of nicotine exposure during adolescence*

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

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 $\beta 2$ 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 $\beta 2^*$ or $\alpha 7^*$ 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 $\alpha 5$ 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.

Figure

