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1 **Do nicotinic receptors modulate high order cognitive processing?**

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8

9 This review is dedicated to the memory of Professor Karl Zilles.

10

11 **Abstract**

12 Recent studies provided strong evidence that deficits in cholinergic signalling cause
13 disorders of cognition and affect conscious processing. Technical advances that combine
14 molecular approaches, *in vivo* recordings in awake behaving animals, human brain imaging and
15 genetics have strengthened our understanding of the roles of nicotinic acetylcholine receptors
16 (nAChRs) in the modulation of cognitive behavior and network dynamics. Here, we review the
17 emergent role of nAChRs in high order cognitive processes and discuss recent work implicating
18 cholinergic circuits in cognitive control, including conscious processing.

19

20 **Keywords:** Nicotinic receptors; conscious processing; prefrontal cortex; anaesthesia;

21 neuropsychiatric disorders; nicotine addiction

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23

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26

27 *Acetylcholine signalling in the brain and neuronal nicotinic receptors*

28 The cholinergic system is a well-organized network of neurons that uses the neurotransmitter
29 acetylcholine (ACh) for intercellular communication and signal transduction. One of the primary
30 roles of ACh in the brain is to coordinate the response of brain networks to internal and external
31 inputs [1] and shape global neuronal activity from multiple brain territories. In particular, ACh
32 plays a key role in orchestrating cortical circuit dynamics during wakefulness and sleep. ACh
33 acts through two classes of receptors: the metabotropic muscarinic receptors and the ionotropic
34 nicotinic receptors. Here, we will focus exclusively on ionotropic nAChR modulation in the
35 brain.

36 Almost all regions of the mammalian brain are innervated by cholinergic inputs with
37 abundant populations of neurons and glial cells expressing nAChRs. The genes encoding for
38 nAChRs are grouped into two families with nine neuronal α -subunits ($\alpha 2$ - $\alpha 10$) and three β -
39 subunits ($\beta 2$ - $\beta 4$) which make different combinations of pentameric oligomers with distinct
40 pharmacological, kinetic and physiological properties. Among the homopentameric nAChRs,
41 receptors composed of one α -subunit category, the $\alpha 7$ -containing subtypes account for the
42 greatest proportion of high affinity α -bungarotoxin binding sites in the mammalian nervous
43 systems (yet with significant contributions of $\alpha 8$ - $\alpha 9$). $\alpha 7$ -containing subtypes are highly
44 expressed in the cortex, hippocampus and limbic areas, whereas lower expression is found in the
45 thalamus and basal ganglia [2]. Among the heteropentameric nAChRs, the $\alpha 4\beta 2$ containing
46 nAChR, which has high affinity for nicotine [3], is the most frequent receptor subtype both in the
47 rodent and human brain. There are many similarities between the distribution of nAChRs in the
48 rodent and primate brain. The most notable differences in nAChRs distribution between these
49 species are those of $\alpha 2$ containing nAChRs [3]. There is also expression of subunits that do not

50 directly contribute to the agonist-binding site, such as the accessory $\alpha 5$ subunit, but play a
51 critical role in the functional properties of the receptor [4].

52 There is a wide variety and distribution of nAChRs in the brain, implying important
53 regional and functional contributions of each nicotinic subunit. The construction of genetically
54 modified mice with deletion of specific nAChR subunits offered exquisite tools to unravel the
55 defined contribution to brain functions of particular subunit types within multi-subunit oligomers
56 [5–8].

57 Nicotinic receptors have been found to be key players in processes such as wakefulness,
58 sleep, and anesthesia, and to contribute to major disorders of the central nervous system, such as
59 Alzheimer’s disease, Parkinson’s disease and schizophrenia as highlighted by studies using
60 biochemical, molecular, imaging and genetic tools. The goal of this review is to discuss recent
61 advances in the understanding of how the diverse nAChRs contribute to cognitive functions and
62 modulate them, both in humans and animal models, ultimately shedding light on the role of
63 nAChRs in the orchestration of higher brain functions.

64

65 *Conscious awareness, wakefulness and sleep*

66 “Qualitative richness, situatedness, intentionality, integration and brain dynamics” are
67 considered as key features of conscious processing [9]. Several nested levels of conscious
68 processing have been recognized which, in humans, develop postnatally and include the
69 awareness of body, self and the relation with physical, social and cultural worlds [10,11].
70 Disturbances of conscious processing are frequently observed in major diseases such as
71 dementia with Lewy bodies, Parkinson’s disease, Alzheimer’s disease and schizophrenia [12–
72 14]. Many theories of conscious processing have been suggested and recently reviewed [15].

73 Among them, the Global Neuronal Workspace (GNW) hypothesis [16] postulates a global
74 computational space composed of widely distributed excitatory neurons with long-range axons,
75 forming a reciprocally connected network. This network was initially suggested to include the
76 dorsolateral prefrontal, inferior parietal and cingulate cortices on top of a set of specialized and
77 modular perceptual, motor, memory, evaluative, and attentional processors. This bidirectional
78 connectivity creates the conditions for “ignition”, which is the triggering of a sudden collective
79 and reverberant coordinated activity that mediates global broadcasting [15,17]. At the neuronal
80 level, the GNW hypothesis posits that large pyramidal cells in cortical layers II/III and pyramidal
81 cells in deeper layer V, together with their thalamic relationships, play a central role in ignition
82 [17].

83 The tuning of sleep-wake cycles is an elaborate process involving the participation of
84 several neurotransmitters and brain structures. Sleep is the only period in which consciousness
85 tones down under physiological conditions, although it has been argued that sleep can still be
86 associated with the presence or absence of conscious experiences [18]. This synergy between the
87 presence and absence of experiences within two types of sleep, non-rapid eye movement sleep
88 (NREM) and rapid eye movement sleep (REM), still poses several questions. Recently,
89 reductions of low-frequency activity in the posterior confluence of sensory and association
90 cortex were associated with dreaming during REM and NREM sleep, but simultaneously, higher
91 frequency gamma activity was detected in frontal and prefrontal cortex [18].

92 The cholinergic system is considered a key player, together with norepinephrine, in
93 modulating REM sleep and contributes to cortical arousal with high levels of ACh release in the
94 forebrain during REM [19] and low levels of neuromodulators during NREM sleep [20,21].
95 Recently, machine learning approaches combined with *in vivo* neurochemical data demonstrated

96 that concentrations of neurotransmitters such as ACh and norepinephrine in prefrontal cortex can
97 predict the levels of cortical and behavioural arousal [22]. Low levels of ACh during NREM
98 sleep has been suggested to enhance synapse formation and episodic/motor memory
99 consolidation mechanisms [23,24].

100 The contribution of nAChRs to the organization of sleep is supported by a study showing
101 that β 2-containing nAChRs modulate the transient phasic activity in NREM, the onset of REM
102 and its duration, and the REM promoting effects of stress [25]. In addition, nicotine intake leads
103 to brain desynchronization and increases arousal and attention [26]. In non-smokers, acute
104 nicotine administration is linked to low REM sleep and slow-wave sleep [27]. In rats, acute
105 nicotine administration increased waking but chronic delivery of nicotine led to higher levels of
106 REM sleep [28]. Treatment with mecamylamine, a non-selective, non-competitive antagonist of
107 nAChRs reversed the sleeping patterns of nicotine treated rats back to normal [28]. Three
108 constitutive mutations of the α 4 subunit, and one mutation of the β 2 subunit of the human
109 nAChR, were linked to a hereditary epileptic syndrome known as autosomal nocturnal frontal
110 lobe epilepsy causing seizures that usually occur at night during sleeping, causing awakening
111 [29–31]. A contribution of nAChRs was also identified in the differential modulation of sleep
112 and wakefulness [25,32,33] and observed deficits in awakening suggested to contribute, among
113 other possibilities, to sudden infant death syndrome [32–34].

114 Evidence exists for the contribution of nAChRs to the modulation of wakefulness and
115 sleep which deserves additional investigation including studies focused on recordings in humans.

116

117 ***Anesthesia***

118 In humans, general anesthesia (GA) is used in patients that undergo surgery for providing
119 analgesia and “loss of consciousness” (LOC), despite reports of anesthesia occasionally causing
120 disconnected states of conscious processing [35] or dream-like states [36]. Mashour and
121 colleagues suggested that LOC is the primary therapeutic action of general anesthesia [15]. There
122 is evidence that GA affects feedback connectivity originating in the frontal areas [37–39], a
123 finding consistent with detailed models of the GNW [17].

124 Even if the mechanism of GA is not fully understood, their direct, stereospecific binding
125 to ligand gated ion channels (LGICs) is considered today as the main mode of action [40]. The
126 superfamily of LGICs includes the inhibitory gamma-aminobutyric acid (GABA), glycine and
127 excitatory 5-hydroxytryptamine (5-HT₃) receptors, with nAChRs being the privileged, though
128 non-exclusive, target for GA in vertebrates causing allosteric modulation of GABA_A receptors.
129 In the case of the bacterial receptor, GLIC (from *Gloeobacter*) [41], propofol and desflurane
130 separately bind to allosteric modulatory sites [41,42].

131 Most general anesthetics inhibit neuronal nAChRs utilizing possible mechanisms
132 including allosteric stabilisation of the closed channel, direct channel blockade, and enhanced
133 desensitization [43]. Each nAChR combination exhibits different sensitivity to general
134 anesthetics, even though they share high sequence homology [44]. The nAChRs oligomers
135 containing $\alpha 4\beta 2$ and $\alpha 3\beta 4$ subunits are the most inhibited nAChRs by volatile anesthetics and
136 ketamine with clinically relevant IC₅₀ values [45]. The $\alpha 4\beta 2$ receptor is affected
137 by isoflurane more potently than the most sensitive GABA_A or glycine receptor, whereas the $\alpha 7$
138 nAChR is not significantly affected by volatile anesthetics or ketamine [46,47].

139 Functional disconnection of the brain due to anesthesia has been studied using
140 neuroimaging techniques in humans and non-human primates. Functional MRI of awake and

141 sedated spontaneous activity in the entire brain of monkeys revealed that under GA the
142 mechanistic relationships between prefrontal, posterior parietal and cingulate cortices – assumed
143 to compose the GNW - are altered [48,49]. In addition, electrocorticography of subjects
144 administered propofol and ketamine in human and nonhuman primates revealed disrupted
145 functional connectivity across primary sensory, motor cortices, and altered beta oscillations,
146 which are associated with feedback processing [15]. Recently, it was demonstrated that wake-
147 like behaviour in rodents could be restored using stimulation of the prefrontal cortex by the
148 cholinergic agonist carbachol in animals that had continuous administration of the general
149 anesthetic sevoflurane, suggesting that cholinergic mechanisms in prefrontal cortex can
150 differentially modulate conscious processing in anesthetized animals [50,51].

151 Recordings performed in humans demonstrated that ongoing spontaneous brain activity
152 forms constant reproducible patterns and exhibits spontaneous ultraslow fluctuations of very low
153 frequency (<0.1 Hz) [52–55] (**Figure 1A**). These ultra-slow neuronal activity patterns are
154 considered as signatures of conscious access [56], and are also observed in animal models [14],
155 yet the neuronal mechanisms of these fluctuations are a matter of debate. *In vivo* recordings in
156 animal models revealed that ultraslow-fluctuations (USFs) persist under general anesthesia with
157 no difference between the percentage of populations that exhibit USFs in the awake state
158 compared to the anesthetized state. However, isoflurane causes a reduction of the synchronously
159 firing populations, thus general anesthesia shows strong inhibitory effects on the generation of
160 neuronal synchrony [14] (**Figure 1B**). It was demonstrated, by recording the ongoing neuronal
161 spontaneous activity of mouse prelimbic cortex, both in the awake and anesthetized (isoflurane)
162 state, that nAChRs play an important role in the generation of USFs, but differently during quiet
163 wakefulness and anesthesia [14] (**Figure 1C**). USFs and neuronal synchronicity are disrupted in

164 genetically modified mice that lack the β 2-nAChRs, but not with α 7 nAChR knockout.
165 Furthermore, pharmacological blockade of β 2 nAChRs suffices to disrupt USFs in awake mice
166 [14] (**Figure 1C**). In addition, light anesthesia using isoflurane was able to disrupt neuronal
167 synchronicity while maintaining the generation of USFs [14]. This is in accordance with recent
168 observations supporting that the anesthetized brain is more dynamic than previously thought with
169 persistent metastable oscillations and patterns that reflect intrinsic dynamics [57,58].

170 In conclusion, important progress in the understanding of the molecular mechanisms of
171 LOC by general anesthetics have been achieved, including defining a contribution of AChRs in
172 the modulation of cortical dynamics and conscious processing.

173

174 *nAChR modulation of high order cognitive processing*

175 The prefrontal cortex is an important component of the GNW which receives dense
176 cholinergic innervation from the basal forebrain and is thought to play a critical role in high
177 order cognitive processes that demand high levels of convergence and integration. Experiments
178 in which cholinergic innervation was removed revealed deficits in attention, whereas stimulation
179 of cholinergic projections led to enhanced attentional performance [59,60]. This finding is
180 consistent with the observation that humans and animal models with lesions to the prefrontal
181 cortex (or prelimbic area) show deficits in attention, working memory and motor behavior. Note
182 that in rodents, the prelimbic area is considered functionally homologous to the dorsolateral
183 prefrontal cortex in humans and non-human primates [61,62].

184 Transgenic mice with deletion of specific nAChR subunits have been an important tool in
185 examining the contribution of nAChRs to cognitive processes [5,7,63]. Mice lacking the β 2-
186 nicotinic subunits (β 2-KO) display similar patterns of social interaction deficits as those caused

187 by lesions in the prelimbic cortex, whereas $\beta 2$ -subunit rescue in $\beta 2$ -KO mice reversed the deficit,
188 indicating that $\beta 2$ -containing nAChRs are necessary for social interactions [64]. A role of $\beta 2$ -
189 nAChRs in motor strategies has been identified as well, with more prominent contribution to
190 exploration than navigation [65]. Of note, exploration typically requires high level cognitive
191 processing, whereas navigation, at least in some of its forms, is more of an automatic behaviour.
192 Genetic deletion of the $\beta 2$ - subunit also resulted in an impairment of attentional performance in a
193 5-choice serial reaction time task [66]. Re-expressing $\beta 2$ -subunits in neurons of the prelimbic
194 cortex restored attentional performance in the same task. By contrast, re-expression of $\beta 2$ -
195 subunits in the adjacent anterior cingulate medial prefrontal cortex did not restore the attentional
196 performance deficits, suggesting that nicotinic modulation of anterior cingulate neurons through
197 $\beta 2$ -containing nAChRs does not modulate attentional behaviour [66]. The same experiments
198 performed in $\alpha 7$ -KO mice showed no effect on attentional performance, suggesting that this
199 function does not depend on the $\alpha 7$ -nicotinic subunit, although previous studies yielded
200 conflicting results [67].

201 In rodents, monkeys and humans, the expression of nAChRs in prefrontal cortex is layer
202 dependent and cell type specific [68] (**Figure 2A**). Recently, it was shown, in awake mice, that
203 endogenous ACh distinctly recruits specific interneurons within a hierarchy that controls
204 pyramidal neuron activity in layers II/III of the prelimbic cortex, through differential expression
205 of nAChRs [69] (**Figure 2B**). Specifically, $\alpha 7$ -KO and $\beta 2$ -KO awake mice exhibit pyramidal
206 cell hyperactivity in layer II/III of prelimbic cortex whereas $\alpha 5$ -KO mice exhibit hypofrontality.
207 Targeted local re-expression of these subunits in defined categories of inhibitory neurons
208 restored the activity to control levels [69]. In addition, a key role of $\alpha 5$ -subunits in attentional
209 performance and social interactions was identified [69,70]. These data highlight the importance

210 of the balance between excitatory and inhibitory neurotransmission (E/I) in the modulation of
211 cognitive functions.

212 The effect of nicotine administration on mental disorders has been documented in several
213 clinical studies. For instance, nicotine is shown to improve attention in schizophrenia patients as
214 well as in nicotine-addicted individuals under craving [26,71,72]. In addition, nicotine decreased
215 depression symptoms, compulsion and anxiety in individuals with attention-deficit hyperactivity
216 disorder or obsessive-compulsive disorder [73,74]. A meta-analysis of 41 placebo controlled
217 studies that included nicotine administration in non-smokers and satiated smokers showed that
218 nicotine had positive effects on short-term episodic memory, working memory performance and
219 motor ability [75]. Another study demonstrated that nicotine can improve working memory in
220 abstinent smokers but not in non-smokers [76]. Imaging studies have been instrumental in
221 identifying brain regions and large-scale networks where nicotine exhibit enhancing effects
222 upon attention, working memory, fine motor skills and episodic memory functions [77].
223 Administration of a $\alpha 4\beta 2$ agonist to monkeys produced improved working memory performance
224 [78]. Recently, ACh stimulation of $\alpha 4\beta 2$ nAChR enhanced the firing of neurons in the prefrontal
225 cortex of primates performing a working memory task [79]. Together, these studies show a
226 unified contribution of nAChRs expressed in the prefrontal cortex to enhance attention, working
227 memory, social behavior and conscious processing in general.

228

229 ***Role of nAChRs in human diseases***

230 Nicotinic receptors have been found to be involved in several disorders of the central
231 nervous system, including Alzheimer's disease, Parkinson's disease and schizophrenia, which
232 we discuss in this section.

233 *Alzheimer's disease*

234 According to the cholinergic hypothesis of Alzheimer's disease (AD), a reduction of
235 cholinergic innervation is responsible (or contributes significantly) to cognitive decline in AD.
236 Building upon this model, inhibitors of acetylcholine-esterase that ameliorate cholinergic
237 signalling [80,81] have been tested as treatments for AD, but they have recently been found of
238 little efficiency in improving mild cognitive impairments and mild AD dementia [82,83].

239 Using post-mortem human samples, it was shown that the $\alpha 7$ -subunit co-localizes with
240 $A\beta_{1-42}$ in amyloid plaques of brain slices obtained from patients with sporadic AD, and
241 immunoprecipitation experiments showed that this interaction is specific for the $\alpha 7$ -subunit
242 [84,85]. Using knock-out mice for the $\alpha 7$ -receptors, researchers attempted to identify a role of
243 the $\alpha 7$ - subunit in AD mouse models, but came to conflicting conclusions regarding the overall
244 pathophysiological contribution of these receptors [86,87]. Specifically, in one of these studies,
245 an AD mouse model that expresses the human amyloid precursor protein with the Swedish and
246 Indiana mutations (associated with early onset of AD) was crossed with $\alpha 7$ -KO mice. Although
247 the AD mice displayed spatial memory deficits, the $\alpha 7$ -KO AD mice were protected against
248 memory impairments [86]. However, in a separate study using a different AD mouse model,
249 cognitive deficits were found to be more severe in AD mice lacking the $\alpha 7$ -nicotinic subunit
250 [87]. It has also been demonstrated that non- $\alpha 7$ -nAChRs, such as $\beta 2$ -containing nAChRs, bind
251 $A\beta$. Electrophysiological and behavioral studies support this interaction [88,89], however, to
252 date it still remains unknown whether $A\beta$ inhibits or activates nAChR and how this interaction
253 may lead to AD pathology.

254 Overall, nAChRs might be key players in the aetiology of AD pathology, and more
255 investigations in both animal models and humans are urgently needed to potentially discover
256 efficient treatments.

257

258 *Parkinson's disease*

259 A hallmark of Parkinson's disease (PD) is the loss of nigrostriatal dopaminergic neurons.
260 Presynaptic and post-synaptic nAChRs modulate dopamine release, and both *in vitro* and *in vivo*
261 animal model studies revealed a crucial role of $\beta 2$ -containing nAChRs in striatal dopaminergic
262 signalling control [90]. Rodent and monkey PD models exhibit a decrease in the levels of
263 nAChR expression in the striatum accompanied by dopaminergic degeneration. Specifically, a
264 loss of $\alpha 6\alpha 4\beta 2\beta 3$ is observed during mild nigrostriatal lesioning, a decrease in $\alpha 6\beta 2\beta 3$
265 receptors is seen when the damage is higher and low levels of $\alpha 4\beta 2$ -containing receptors when
266 the degeneration is extremely severe [90]. Similarly, decreased expression of nAChR is found in
267 the caudate, putamen and substantia nigra of humans affected by PD and this decrease is linked
268 to the level of nigrostriatal damage [91].

269 Nicotine is found to reduce levodopa-induced dyskinesias, a major side effect of
270 levodopa therapy, improves motor abilities in PD patients and protects against nigrostriatal
271 damage [92,93], pointing at nicotine and nicotinic agonists as promising candidates as part of a
272 treatment regimen for PD.

273

274 *Schizophrenia*

275 Schizophrenia is a neuropsychiatric disorder that is characterized by both positive
276 symptoms (e.g. hallucinations and delusions) and negative ones (e.g. flattened affect) that usually

277 begin in late adolescence or early adulthood [94]. A distinct role of nAChR subunits in
278 schizophrenia has been initially shown by identifying decreased levels of $\alpha 7$ -nAChRs in post-
279 mortem hippocampus [95], cortex [96] and in the thalamus of schizophrenia patients [97]. Also,
280 there is evidence that the expression of $\alpha 4\beta 2$ -containing-nAChRs, as determined by 3H-nicotine
281 binding, is reduced in the hippocampus of these patients [98].

282 The prevalence of smoking among schizophrenia patients is three to five times higher
283 than in the general population [99] and schizophrenia patients extract 50% more nicotine per
284 cigarette than other smokers, by inhaling more deeply [100]. The aetiology of this prevalence of
285 smoking among schizophrenia patients is not yet understood and several mechanisms have been
286 suggested. Among them, it has been proposed that nicotine serves as a form of self-medication to
287 alleviate the negative symptoms of the disease, enhance cognitive deficits or reduce the side
288 effects of antipsychotic treatments. At variance with this interpretation, it was suggested that
289 cigarette smoking might be itself a cause of psychosis [101]. Large, longitudinal, prospective
290 studies are needed to investigate the relationship between smoking and psychosis in order to be
291 able to elucidate whether cigarette smoking has a causal role or not in the development of
292 psychosis [102].

293 Schizophrenia patients develop multiple sensory processing deficits including auditory
294 sensory processing (P50) impairments, pre-pulse inhibition (PPI) reductions, and eye-tracking
295 deficiencies [103]. P50 gating impairments have been linked to the chromosome 15q13-14 site of
296 the *CHRNA7* gene [104]. Interestingly, it has been shown that in schizophrenia patients nicotine
297 normalizes the P50 gating deficits and that treatment of mice with $\alpha 7$ -nAChR agonists corrects
298 the sensory gating anomalies [103,105,106]. Activation of $\alpha 7$ -nAChRs by nicotine or nicotinic

299 agonists increases glutamate release and in turn normalized P50 gating deficits [107]. Moreover,
300 patients with schizophrenia exhibit reduced PPI and eye-tracking deficits, although nicotine
301 intake increases PPI and eye-tracking performance in these patients [108–110]. Finally, studies
302 in animal models, but also in humans, found that nicotine improves cognitive functions such as
303 working memory, attention and social interactions, which are impaired in schizophrenia patients
304 [105].

305 In conclusion, clinical trials of nicotinic agonists but also positive allosteric modulators
306 of defined nAChR oligomers are of crucial importance to develop potential treatments of
307 psychiatric disorders such as schizophrenia.

308

309 *Genetic studies on the contribution of nAChR to human diseases*

310 Genome-wide association studies (GWAS) identified susceptible loci in specific diseases
311 by screening millions of genetic factors in cohorts of thousands of patients and controls. This
312 strategy may help the development of personalized medicine approaches based on the evaluation
313 of genetic risks. Genetic variations in nAChRs subunits have been found to be strongly
314 associated with complex neuropsychiatric diseases such as schizophrenia and a number of
315 Mendelian disorders (**Box 1**).

316

317 *Loss of control in Nicotine addiction*

318 Subjects addicted to drugs such as nicotine or cocaine reveal neural circuit impairments
319 associated with disruptions of the dopaminergic system [111]. Drug addiction causes a marked
320 dysregulation of brain circuits involved in reward, motivation, memory, judgment and self-
321 awareness, including circuits in frontal cortical regions. These deficits cause a compulsive self-

322 administration of drug with a loss of control (altered inhibition) and disrupted cognitive
323 operations that impair judgment and favor relapse [5,111,112]. Behavioural differences and
324 increased dopamine release in response to nicotine leads to greater likelihood of addiction
325 occurring in adolescents compared with adults, and long-lasting dysregulation of attention and
326 sensory processing [113,114]. Several molecular changes are taking place as a consequence of
327 chronic nicotine exposure such as upregulation of $\alpha 7$ -nAChRs, increased presynaptic $\alpha 7$ -nAChR
328 transmission, upregulation of $\beta 2$ - nAChRs, presynaptic downregulation of $\beta 2$ -nAChRs and
329 increased dopaminergic neuron activity [5]. An effect of nicotine and ACh on axon excitability
330 was also described, indicating that nAChRs are probably located at nodes of Ranvier in
331 particular along myelinated thalamocortical axons [115,116], revealing a non-synaptic action of
332 nicotinic agents. Human individuals addicted to nicotine exhibit cognitive deficits similar to
333 those of patients with an impaired ventromedial prefrontal cortex [117].

334 Functional MRI studies in rodents have shown that, consistent with the enhancing effect
335 of nicotine, *acute* injections of nicotine increased the activation of prelimbic, frontal motor and
336 somatosensory cortices as well as the nucleus accumbens, ventral tegmental area, substantia
337 nigra and thalamus [118]. *Chronic* administration of nicotine produces pyramidal cell
338 hyperactivity in the prefrontal cortex of awake mice [69]. Moreover, mice expressing a human
339 polymorphism in the $\alpha 5$ nicotinic subunit (rs16969968_ $\alpha 5$ SNP), which is associated with
340 nicotine addiction and schizophrenia, exhibit reduced pyramidal cell activity in layer II/III of
341 prelimbic cortex compared to wild-type control mice due to alterations in the balance between
342 excitation and inhibition [69] (**Figure 2B**). Interestingly, chronic administration of nicotine
343 through an osmotic minipump was able to restore the hypofrontality associated with the $\alpha 5$ SNP,
344 suggesting an explanation of why individuals with schizophrenia may use tobacco smoking as a

345 form of self-medication [69] (**Figure 2B**). Similarly, humans with the $\alpha 5$ SNP exhibit reduced
346 resting state functional connectivity and altered prefrontal cortex circuitry [119] (**Figure 3 and**
347 **Box 1**).

348 Neuroimaging techniques reveal that in smokers, $\alpha 4\beta 2$ -containing nAChRs are
349 upregulated compared to non-smoking individuals. Furthermore abstinence for 3 to 12 weeks can
350 normalize the receptor levels to that of non-smokers [120,121]. Yet the possible relationship of
351 these changes to long-term loss of inhibitory control is still not understood.

352 Tobacco smoking is robustly linked to epigenetic modifications. In smokers, DNA
353 methylation changes take place at several genomic loci, mainly at cytosine-phosphate-guanine
354 sites [122,123]. At most of the loci, smoking causes loss of methylation to the extent that
355 epigenome profiling of DNA methylation patterns associated with tobacco smoking can serve as
356 molecular biomarkers for major diseases such as lung cancer [124]. Exposure to nicotine during
357 prenatal and early postnatal periods is claimed to cause abnormal development of the brain and
358 favors the onset of mental disorders [125]. This is of particular importance since in some
359 countries, up to about 10% of women smoke during pregnancy, thereby exposing their offspring
360 to nicotine during critical neurodevelopmental periods [125]. Early nicotine exposure produces
361 long lasting impairments in neuronal plasticity such as increased spine density and branching in
362 the frontal, medial and caudal cerebral cortex [126]. Recently, it was demonstrated that
363 activation of heteropentameric nAChRs by early nicotine exposure causes alterations in histone
364 methylation in the cerebral cortex, which in turn increases the expression of genes involved in
365 synapse maintenance and dendritic remodeling together with behavioral alterations such as
366 hypersensitive passive avoidance performance [126].

367 These studies reveal a *dual action* of nicotine as a drug; a positive, therapeutic role as a
368 cognitive stimulant and a negative effect as an addictive drug causing loss of control in drug
369 consumption and other cognitive impairments.

370

371 ***Concluding remarks***

372 The neuronal and molecular mechanisms involved in modulating high order cognitive
373 functions, and more specifically, conscious processing, remain one of the most intriguing issues
374 of research in neuroscience. Yet substantial progress has been achieved over the last decades in
375 the identification of the molecular components of the circuit engaged in cognition and its
376 dysfunctions, both in animal models and in humans. In particular, deciphering the modulatory
377 mechanisms of awareness, sleep, anesthesia, LOC and mental disorders has contributed to our
378 improved understanding of the conscious processes involved.

379 It is our opinion that through the use of a broad range of methods, including genetically
380 modified animals and brain imaging in humans, the evidence is clear that nAChRs do modulate
381 high order cognitive functions, including conscious processing. Thanks to investigations of
382 nAChRs – among other receptors - a “pharmacology of consciousness” becomes scientifically
383 accessible thereby opening multiple novel strategies for the diagnosis, prevention and therapies
384 of neuropsychiatric diseases (see **Outstanding Questions**).

385

386

387 **Box 1. Human genetic studies identify variants of nAChRs linked to major psychiatric**
388 **disorders.**

389 *The CHRNA5/CHRNA3/CHRNA4 gene cluster*

390 The 15q25 gene cluster, which contains the *CHRNA5/CHRNA3/CHRNA4* genes, coding for the
391 $\alpha 5$ -, $\alpha 3$ - and $\beta 4$ -nAChR subunits, was associated with risk for heavy smoking and nicotine
392 addiction [127–132] and several single nucleotide polymorphisms (SNPs) were identified [130–
393 133]. The non-synonymous SNP rs16969968, found in exon 5 of the $\alpha 5$ -human gene, involves a
394 substitution of an aspartic acid by an asparagine in position 398 (D398N). The $\alpha 5$ SNP is present
395 in about 35% of Europeans and 50% of Middle Eastern populations and has been linked to
396 nicotine dependence, lower ratings of aversive effect, delayed smoking cessation, early lung
397 cancer and cognitive improvement after nicotine intake [127,134]. Recently, the same genetic
398 locus was associated with schizophrenia in a major GWAS study [135]. The $\alpha 5$ SNP is linked to
399 schizophrenia in both Caucasian and African-American patients and is associated with decreased
400 intrinsic resting functional connectivity (rsFC) in humans [119] (**Figure 3**). Mice with this
401 polymorphism exhibit schizophrenia related cognitive deficits and hypofrontality that is reversed
402 after chronic nicotine administration [69]. In addition to nicotine dependence and schizophrenia,
403 the 15q25 gene cluster has been associated with alcohol, cocaine and opioid dependence,
404 suggesting a potential association with substance use disorders in general [128]. However, the
405 same rs16969968_ $\alpha 5$ SNP has been linked to lower prevalence of cocaine use disorder in
406 humans [128].

407 Interestingly, rare (<5%) missense variants at conserved sites in *CHRNA4* are associated with
408 decreased risk of developing nicotine dependence and decrease the number of cigarettes
409 consumed daily by smokers [136].

410 *The human CHRNA7 and CHRFA7A genes*

411 The human *CHRNA7* gene has 10 exons and is located on the long arm of chromosome 15q13-
412 q14), which is a highly unstable area of the human genome that is linked to schizophrenia. A
413 polymorphism in the 5' -regulatory region (not duplicated) of *CHRNA7* (rs3087454) was found
414 to be strongly associated with schizophrenia [137,138]. However, there is no convincing
415 evidence associating the *CHRNA7* gene with smoking [139–141].

416 In humans, gene duplication in exons 5-10 in *CHRNA7* during evolution produced a hybrid gene,
417 *CHRFA7A*. The duplication is human specific, found neither in primates nor in rodents, but a
418 similar sequence has been identified in gorillas [142]. Its product, referred as dupa7, lacks part of
419 the N-terminal extracellular ligand-binding domain and it is linked to many neuropsychiatric
420 conditions. Dup7 is considered a dominant-negative regulator of ion channel function [143]. It
421 was suggested that increased expression of the *CHRFA7A* gene in patients with schizophrenia
422 might contribute to failure to regulate nicotine binding to high affinity nicotinic receptors. In
423 addition, a 2 bp deletion was identified in exon 6 of the *CHRFA7A* gene [144]. This deletion is
424 more common in Caucasians than African-Americans and is a more potent negative regulator of
425 $\alpha 7$ -nAChR function than the normal copy and it was linked to both bipolar disorder and
426 schizophrenia [143].

427 The *CHRFA7A* gene can vary in copy number with individuals with one copy or none and
428 deletions of the *CHRNA7* and *CHRFA7A* are strongly associated with schizophrenia [145,146].
429 In addition, rare deletions and duplication of the same area have been linked to autism, epilepsy,

430 bipolar disorder and attention deficit hyperactivity disorder [147]. A recent study that used
431 induced pluripotent cells and neural progenitor cells derived from individuals with heterozygous
432 15q13.3 deletions and duplications demonstrated that calcium signal cascades that are dependent
433 on $\alpha 7$ -nAChRs are downregulated suggesting that individuals with deletions and duplications of
434 15q13.3 exhibit cognitive deficits [148].

435 *The CHRNA2, CHRNA4 and CHRNB2 genes*

436 Missense mutations or indels in *CHRNA2*, *CHRNA4* and *CHRNB2* genes have been linked to
437 autosomal dominant nocturnal frontal lobe seizures which usually occur during non-rapid eye
438 movement sleep [149].

439

440 **Figure legends**

441 **Figure 1. Ultra-slow fluctuations (USFs) as a signature of conscious processing.**

442 **A)** USFs (< 0.1 HZ) in neuronal activity of human auditory cortex from the right (red) and left
443 (blue) hemispheres during wakefulness in the absence of auditory stimulation. Anatomical
444 locations of auditory electrodes for three patients are indicated with three different colors (red,
445 blue and green). The vertical lines indicate spike times and the black arrows point out the
446 relationship between time courses of slow fluctuations and spikes. The waveforms of neuronal
447 action potentials are shown below the spike trains. Adapted from [55]. **B)** USFs identified in
448 mouse PFC spontaneous neuronal activity under light anaesthesia and in the awake state. Each
449 raster plot indicates one population of simultaneously recorded neurons in wild-type mice in the
450 awake and anesthetized state using *in vivo* two-photon calcium imaging in head-fixed mice. Each
451 row corresponds to the spiking activity of one neuron. Adapted from [14]. **C)** $\beta 2$ -KO mice and
452 chronic exposure to mecamylamine (non-selective antagonist of nAChRs) are characterized by

453 reductions in the percentage of cells that exhibit USFs, indicating a major role of nAChRs in the
454 generation of the physiological phenomena that are linked to conscious processing. The raster
455 plots represent neuronal activity during wakefulness. Adapted from [14].

456

457 **Figure 2. Nicotinic receptor modulation of PFC circuit dynamics involved in schizophrenia**
458 **and nicotine addiction.**

459 **A)** The expression of nicotinic receptors in prefrontal cortex is layer dependent and neuronal
460 type specific. The $\alpha 7$ - and $\beta 2$ -nicotinic subunits are highly expressed and the $\alpha 5$ -nicotinic
461 subunit is expressed at a lower extent. Almost no pyramidal neurons (P) in layer II/III of
462 prefrontal cortex express nAChRs, whereas the pyramidal neurons of layer V mouse prefrontal
463 cortex exhibit fast nAChR currents that are mediated by $\alpha 7$ -containing nAChRs. Both human
464 and mouse layer VI pyramidal neurons express $\alpha 5$ - and $\beta 2$ -containing nAChRs. Modified from
465 [150] based on [69,151–154]. **B)** In layer II/III of mouse prelimbic cortex, $\alpha 5$ -containing
466 nAChRs are expressed by vasoactive intestinal polypeptide (VIP) interneurons, somatostatin
467 (SOM) interneurons express $\alpha 7$ - and $\beta 2$ -containing nAChRs, whereas parvalbumin (PV) fast
468 spiking neurons express $\alpha 7$ -nAChRs [69,151,152]. $\alpha 5$ -containing nAChRs control the VIP-
469 mediated disinhibition via SOM interneuron inhibition of pyramidal neurons in layers II/III in
470 prelimbic cortex [69]. **C)** The $\alpha 5$ SNP, a human polymorphism linked to nicotine addiction and
471 schizophrenia, decreases the activity of VIP interneurons. This leads to increased SOM
472 interneuron activity that, in turn, reduces pyramidal neuron activity, resulting in hypofrontality, a
473 feature of schizophrenia. **D)** Chronic nicotine administration desensitizes $\beta 2$ -containing nAChRs
474 on SOM interneurons. As a result, SOM inhibition of pyramidal neurons is reduced and the
475 activity is normalized. Modified from [69,155].

476

477 **Figure 3. Brain imaging of resting states by MRI of human nAChR genetic variants. A)** The
478 $\alpha 5$ SNP (Asp3898Asn) is associated with a dorsal anterior cingulate (dACC)-ventral
479 striatum/extended amygdala circuit and decreases the intrinsic resting state functional
480 connectivity strength in this circuit, where eight brain regions are involved (the different regions
481 are indicated with different colors). Regions 1 and 2; right and left ventral striatum/substantia
482 innominata/extended amygdala/hippocampus, 3; orbitofrontal cortex, 4; rostral cingulate, 5;
483 middle cingulate, 6; middle temporal cortex, 7; precuneus and 8; cuneus. **B)** Coronal section of
484 regions 1 and 2, which are the two largest regions. Their connectivity with the dACC (red area)
485 is associated with the $\alpha 5$ SNP, smoking and nicotine addiction severity. The arrows point to the
486 functional connectivity between the dACC and areas 1 and 2 but do not indicate directionality.
487 **C)** The human genotype effect on the eight circuits. The risk allele Asn of Asp398Asn was
488 associated with significantly reduced functional connectivity between dACC and the eight brain
489 regions ($P < 0.05$). (A-C) Adapted from [119].

490

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496

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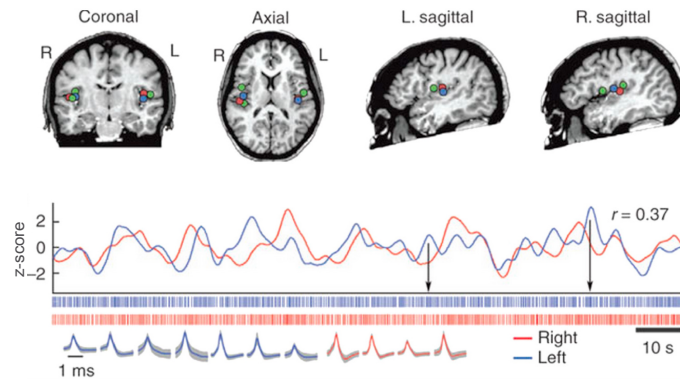
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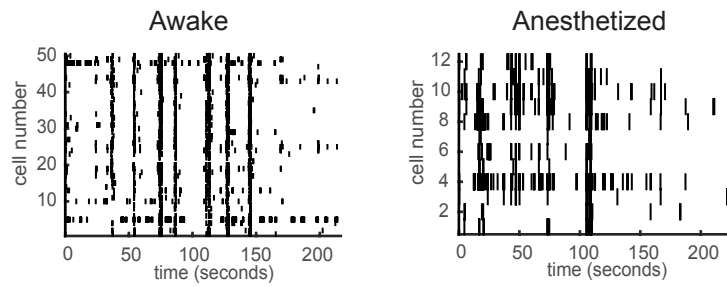
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A Ultra-slow fluctuations in human brain



B Ultra-slow fluctuations in mouse PFC



C Spontaneous ignition under nAChR control

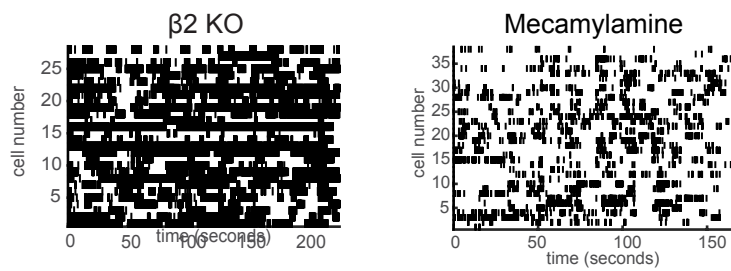


Figure 1

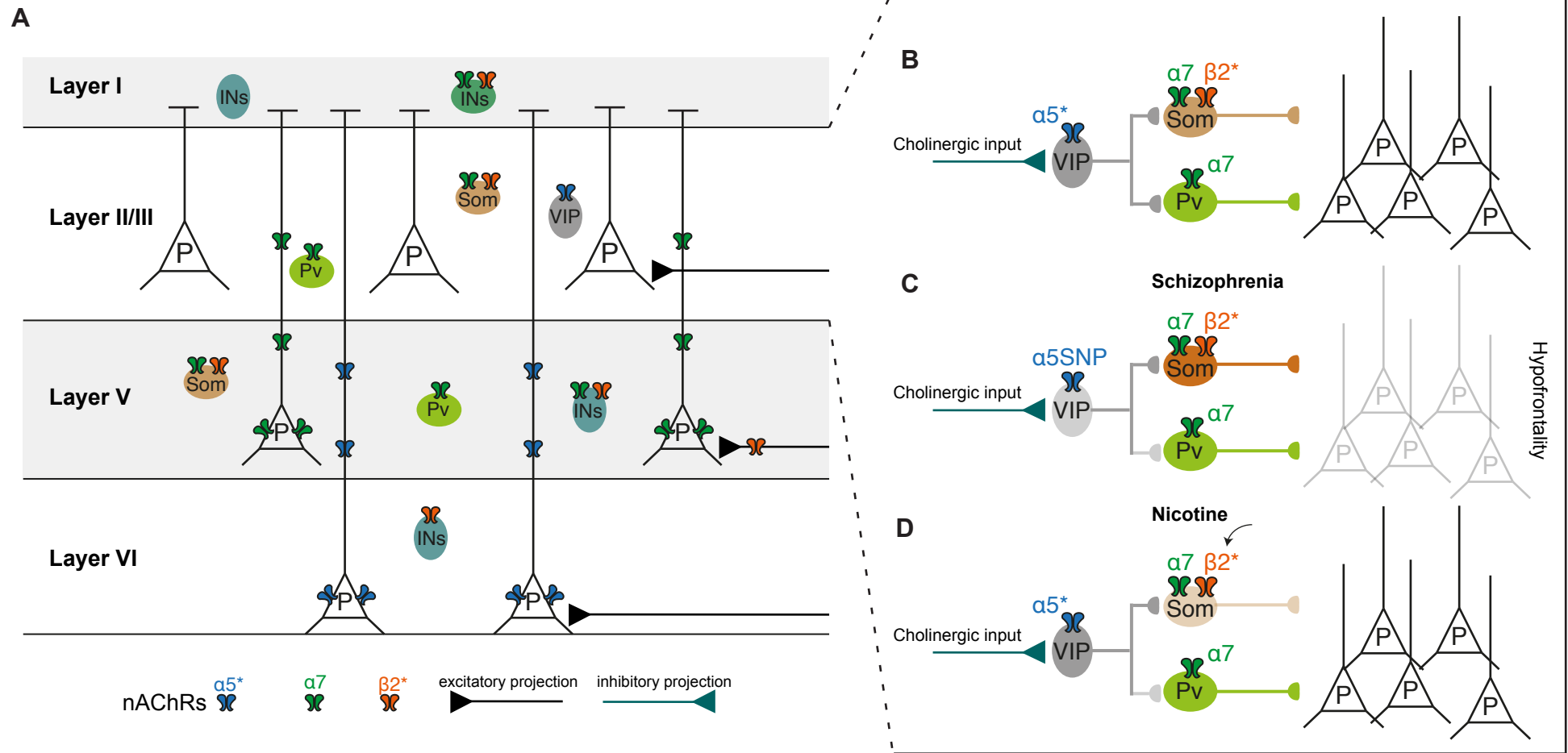


Figure 2

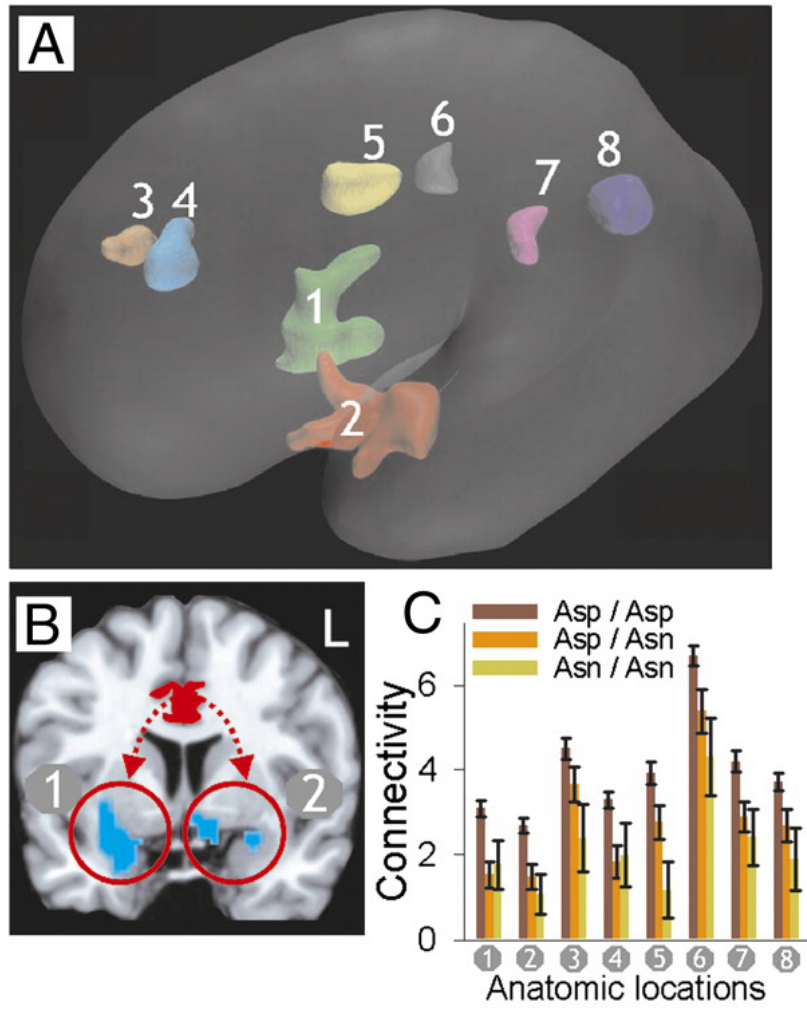


Figure 3