Opinion

Do Nicotinic Receptors Modulate High-Order Cognitive Processing?☆

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

Acetylcholine Signaling in the Brain and Neuronal Nicotinic Receptors

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

Almost all regions of the mammalian brain are innervated by cholinergic inputs with abundant populations of neurons and glial cells expressing nAChRs. The genes encoding for nAChRs are grouped into two families with nine neuronal α-subunits (α2–α10) and three β-subunits (β2–β4), which make different combinations of pentameric oligomers with distinct pharmacological, kinetic, and physiological properties. Among the homopentameric nAChRs, receptors composed of one α-subunit category, the α7-containing subtypes account for the greatest proportion of high affinity α-bungarotoxin binding sites in the mammalian nervous systems (yet with significant contributions of α8–α9). α7-containing subtypes are highly expressed in the cortex, hippocampus, and limbic areas, whereas lower expression is found in the thalamus and basal ganglia [2]. Among the heteropentameric nAChRs, the α4β2 containing nAChR, which has high affinity for nicotine [3], is the most frequent receptor subtype both in the rodent and human brain. There are many similarities between the distribution of nAChRs in the rodent and primate brain. The most notable differences in nAChR distribution between these species are those of α2-containing nAChRs [3]. There is also expression of subunits that do not directly contribute to the agonist-binding site, such as the accessory c5-subunit, but play a critical role in the functional properties of the receptor [4].

There is a wide variety and distribution of nAChRs in the brain, implying important regional and functional contributions of each nicotinic subunit. The construction of genetically modified mice with deletion of specific nAChR subunits offered exquisite tools to unravel the defined contribution to brain functions of particular subunit types within multi-subunit oligomers [5–8].
Nicotinic receptors have been found to be key players in processes such as wakefulness, sleep, and anesthesia, and to contribute to major disorders of the central nervous system, such as Alzheimer’s disease (AD), Parkinson’s disease (PD), and schizophrenia, as highlighted by studies using biochemical, molecular, imaging, and genetic tools. The goal of this review is to discuss recent advances in the understanding of how the diverse nAChRs contribute to cognitive functions and modulate them, both in humans and animal models, ultimately shedding light on the role of nAChRs in the orchestration of higher brain functions.

Conscious Awareness, Wakefulness, and Sleep

‘Qualitative richness, situatedness, intentionality, integration and brain dynamics’ are considered as key features of conscious processing [9]. Several nested levels of conscious processing have been recognized, which, in humans, develop postnatally and include the awareness of body, self, and the relation with physical, social, and cultural worlds [10,11]. Disturbances of conscious processing are frequently observed in major diseases such as dementia with Lewy bodies, PD, AD, and schizophrenia [12–14]. Many theories of conscious processing have been suggested and recently reviewed [15]. Among them, the global neuronal workspace (GNW) hypothesis [16] postulates a global computational space composed of widely distributed excitatory neurons with long-range axons, forming a reciprocally connected network. This network was initially suggested to include the dorsolateral prefrontal, inferior parietal, and cingulate cortices on top of a set of specialized and modular perceptual, motor, memory, evaluative, and attentional processors. This bidirectional connectivity creates the conditions for ‘ignition’, which is the triggering of a sudden collective and reverberant coordinated activity that mediates global broadcasting [15,17]. At the neuronal level, the GNW hypothesis posits that large pyramidal cells in cortical layers II/III and pyramidal cells in deeper layer V, together with their thalamic relationships, play a central role in ignition [17].

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

The cholinergic system is considered a key player, together with norepinephrine, in modulating REM sleep and contributes to cortical arousal with high levels of ACh release in the forebrain during REM [19] and low levels of neuromodulators during NREM sleep [20,21]. Recently, machine learning approaches combined with in vivo neurochemical data demonstrated that concentrations of neurotransmitters such as ACh and norepinephrine in prefrontal cortex can predict the levels of cortical and behavioral arousal [22]. Low levels of ACh during NREM sleep have been suggested to enhance synapse formation and episodic/motor memory consolidation mechanisms [23,24].

The contribution of nAChRs to the organization of sleep is supported by a study showing that β2-containing nAChRs modulate the transient phasic activity in NREM, the onset of REM and its duration, and the REM promoting effects of stress [25]. In addition, nicotine intake leads to brain desynchronization and increases arousal and attention [26]. In nonsmokers, acute nicotine administration is linked to low REM sleep and slow-wave sleep [27]. In rats, acute nicotine...
administration increased waking but chronic delivery of nicotine led to higher levels of REM sleep [28]. Treatment with mecamylamine, a nonselective, noncompetitive antagonist of nAChRs, reversed the sleeping patterns of nicotine-treated rats back to normal [28]. Three constitutive mutations of the α4 subunit, and one mutation of the β2 subunit of the human nAChR, were linked to a hereditary epileptic syndrome known as autosomal nocturnal frontal lobe epilepsy causing seizures that usually occur at night during sleeping, causing awakening [29–31]. A role of nAChRs was also identified in the differential modulation of sleep and wakefulness [25,32,33] and observed deficits in awakening suggested to contribute, among other possibilities, to sudden infant death syndrome [32–34].

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

**Anesthesia**

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

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

Most general anesthetics inhibit neuronal nAChRs, utilizing possible mechanisms including allosteric stabilization of the closed channel, direct channel blockade, and enhanced desensitization [43]. Each nAChR combination exhibits different sensitivity to general anesthetics, even though they share high sequence homology [44]. The nAChR oligomers containing α4β2 and α3β4 subunits are the most inhibited nAChRs by volatile anesthetics and ketamine, with clinically relevant IC50 values [45]. The α4β2 receptor is affected by isoflurane more potently than the most sensitive GABA_A or glycine receptor, whereas the α7 nAChR is not significantly affected by volatile anesthetics or ketamine [46,47].

Functional disconnection of the brain due to anesthesia has been studied using neuroimaging techniques in humans and non-human primates. Functional magnetic resonance imaging (fMRI) of awake and sedated spontaneous activity in the entire brain of monkeys revealed that under GA the mechanistic relationships between prefrontal, posterior parietal, and cingulate cortices, assumed to compose the GNW, are altered [48,49]. In addition, electrocorticography of subjects administered propofol and ketamine in human and non-human primates revealed disrupted functional connectivity across primary sensory, motor cortices, and altered beta oscillations, which are associated with feedback processing [15]. Recently, it was demonstrated that wake-like behavior in rodents could be restored using stimulation of the prefrontal cortex by the cholinergic agonist carbachol in animals that had continuous administration of the general anesthetic sevoflurane, suggesting that cholinergic mechanisms in prefrontal cortex can differentially modulate conscious processing in anesthetized animals [50,51].
Recordings performed in humans demonstrated that ongoing spontaneous brain activity forms constant reproducible patterns and exhibits spontaneous ultraslow fluctuations of very low frequency (<0.1 Hz) [52–55] (Figure 1A). These ultra-slow neuronal activity patterns are considered as signatures of conscious access [56] and are also observed in animal models [14], yet the neuronal mechanisms of these fluctuations are a matter of debate. In vivo recordings in animal models revealed that ultraslow fluctuations (USFs) persist under GA with no difference between the percentage of populations that exhibit USFs in the awake state compared with the anesthetized state. However, isoflurane causes a reduction of the synchronously firing populations, thus GA shows strong inhibitory effects on the generation of neuronal synchrony [14] (Figure 1B). It was demonstrated, by recording the ongoing neuronal spontaneous activity of mouse prelimbic cortex, both in the awake and anesthetized (isoflurane) state, that nAChRs play an important role in the generation of USFs, but differently during quiet wakefulness and anesthesia [14] (Figure 1C). USFs and neuronal synchronicty are disrupted in genetically modified mice that lack the β2-nAChRs, but not with α7 nAChR knockout (KO). Furthermore, pharmacological blockade of β2-nAChRs suffices to disrupt USFs in awake mice [14] (Figure 1C). In addition, light anesthesia using isoflurane was able to disrupt neuronal synchronicty while maintaining the generation of USFs [14]. This is in accordance with recent observations supporting that the anesthetized brain is more dynamic than previously thought, with persistent metastable oscillations and patterns that reflect intrinsic dynamics [57,58].

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

nAChR Modulation of High-Order Cognitive Processing

The prefrontal cortex is an important component of the GNW that receives dense cholinergic innervation from the basal forebrain and is thought to play a critical role in high-order cognitive processes that demand high levels of convergence and integration. Experiments in which cholinergic innervation was removed revealed deficits in attention, whereas stimulation of cholinergic projections led to enhanced attentional performance [59,60]. This finding is consistent with the observation that humans and animal models with lesions to the prefrontal cortex (or prelimbic area) show deficits in attention, working memory, and motor behavior. Note that in rodents, the prelimbic area is considered functionally homologous to the dorsolateral prefrontal cortex in humans and non-human primates [61,62]. Transgenic mice with deletion of specific nAChR subunits have been an important tool in examining the contribution of nAChRs to cognitive processes [5–7]. Mice lacking the β2-nicotinic subunits (β2-KO) display similar patterns of social interaction deficits as those caused by lesions in the prelimbic cortex, whereas β2-subunit rescue in β2-KO mice reversed the deficit, indicating that β2-containing nAChRs are necessary for social interactions [63]. A role of β2-nAChRs in motor strategies has been identified as well, with more prominent contribution to exploration than navigation [64]. Of note, exploration typically requires high-level cognitive processing, whereas navigation, at least in some of its forms, is more of an automatic behavior. Genetic deletion of the β2-subunit also resulted in an impairment of attentional performance in a five-choice serial reaction time task [65]. Re-expressing β2-subunits in neurons of the prelimbic cortex restored attentional performance in the same task. By contrast, re-expression of β2-subunits in the adjacent anterior cingulate cortex did not restore the attentional performance deficits, suggesting that nicotinic modulation of anterior cingulate neurons through β2-containing nAChRs does not modulate attentional behavior [65]. The same experiments performed in α7-KO mice showed no effect on attentional performance, suggesting that this function does not depend on the α7-nicotinic subunit, although previous studies yielded conflicting results [66].
(A) Ultra-slow fluctuations in human brain

(B) Ultra-slow fluctuations in mouse PFC

(C) Spontaneous ignition under nAChR control

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In rodents, monkeys, and humans, the expression of nAChRs in prefrontal cortex is layer dependent and cell type specific [67] (Figure 2A). Recently, it was shown, in awake mice, that endogenous ACh distinctly recruits specific interneurons within a hierarchy that controls pyramidal neuron activity in layers II/III of the prelimbic cortex, through differential expression of nAChRs [68] (Figure 2B). Specifically, α7-KO and β2-KO awake mice exhibit pyramidal cell hyperactivity in layer II/III of prelimbic cortex, whereas α5-KO mice exhibit hypofrontality. Targeted local re-expression of these subunits in defined categories of inhibitory neurons restored the activity to control levels [68]. In addition, a key role of α5-subunits in attentional performance and social interactions was identified [68,69]. These data highlight the importance of the balance between excitatory and inhibitory neurotransmission (E/I) in the modulation of cognitive functions.

The effect of nicotine administration on mental disorders has been documented in several clinical studies. For instance, nicotine is shown to improve attention in schizophrenia patients as well as in nicotine-addicted individuals under craving [26,70,71]. In addition, nicotine decreased depression symptoms, compulsion, and anxiety in individuals with attention-deficit hyperactivity disorder or obsessive-compulsive disorder [72,73]. A meta-analysis of 41 placebo controlled studies that included nicotine administration in nonsmokers and satiated smokers showed that nicotine had positive effects on short-term episodic memory, working memory performance, and motor ability [74]. Another study demonstrated that nicotine can improve working memory in abstinent smokers but not in nonsmokers [75]. Imaging studies have been instrumental in identifying brain regions and large-scale networks where nicotine exhibits enhancing effects upon attention, working memory, fine motor skills, and episodic memory functions [76]. Administration of a α4β2 agonist to monkeys produced improved working memory performance [77]. Recently, ACh stimulation of α4β2 nAChR enhanced the firing of neurons in the prefrontal cortex of primates performing a working memory task [78]. Together, these studies show a unified contribution of nAChRs expressed in the prefrontal cortex to enhance attention, working memory, social behavior, and conscious processing in general.

Role of nAChRs in Human Diseases

Nicotinic receptors have been found to be involved in several disorders of the central nervous system, including AD, PD, and schizophrenia, which we discuss in this section.

AD

According to the cholinergic hypothesis of AD, a reduction of cholinergic innervation is responsible (or contributes significantly) to cognitive decline in AD. Building upon this model, inhibitors of ACh-esterase that ameliorate cholinergic signaling [79,80] have been tested as treatments for AD, but they have recently been found of little efficiency in improving mild cognitive impairments and mild AD dementia [81,82].

Figure 1. Ultra-Slow Fluctuations (USFs) as a Signature of Conscious Processing. (A) USFs (<0.1 Hz) in neuronal activity of human auditory cortex from the right (red) and left (blue) hemispheres during wakefulness in the absence of auditory stimulation. Anatomical locations of auditory electrodes for three patients are indicated with three different colors (red, blue, and green). The vertical lines indicate spike times and the black arrows point out the relationship between time courses of slow fluctuations and spikes. The waveforms of neuronal action potentials are shown below the spike trains. Adapted from [55]. (B) USFs identified in mouse prefrontal cortex (PFC) spontaneous neuronal activity in the awake state and under light anesthesia. Each raster plot indicates one population of simultaneously recorded neurons in wild type mice in the awake and anesthetized state using in vivo two-photon calcium imaging in head-fixed mice. Each row corresponds to the spiking activity of one neuron. Adapted from [14]. (C) β2-knockout (KO) mice and chronic exposure to mecamylamine [nonselective antagonist of nicotinic acetylcholine receptors (nAChRs)] are characterized by reductions in the percentage of cells that exhibit USFs, indicating a major role of nAChRs in the generation of the physiological phenomena that are linked to conscious processing. The raster plots represent neuronal activity during wakefulness. Adapted from [14].
Using postmortem human samples, it was shown that the α7-subunit colocalizes with Aβ1-42 in amyloid plaques of brain slices obtained from patients with sporadic AD and immunoprecipitation experiments showed that this interaction is specific for the α7-subunit [83,84]. Using KO mice for the α7-receptors, researchers attempted to identify a role of the α7-subunit in AD mouse models, but came to conflicting conclusions regarding the overall pathophysiological contribution of these receptors [85,86]. Specifically, in one of these studies, an AD mouse model that expresses the human amyloid precursor protein with the Swedish and Indiana mutations (associated with early onset of AD) was crossed with α7-KO mice. Although the AD mice displayed spatial memory deficits, the α7-KO AD mice were protected against memory impairments [85]. However, in a separate study using a different AD mouse model, cognitive deficits were found to be more severe in AD mice lacking the α7-nicotinic subunit [86]. It has also been demonstrated that non-α7-nAChRs, such as β2-containing nAChRs, bind Aβ. Electrophysiological and behavioral studies support this interaction [87,88], however, to date it still remains unknown whether Aβ inhibits or activates nAChR and how this interaction may lead to AD pathology.

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

Figure 2. Nicotinic Receptor Modulation of Prefrontal Cortex (PFC) Circuit Dynamics Involved in Schizophrenia and Nicotine Addiction. (A) The expression of nicotinic receptors in prefrontal cortex is layer dependent and neuronal type specific. The α7- and β2-nicotinic subunits are highly expressed and the α5-nicotinic subunit is expressed at a lower extent. Nicotinic acetylcholine receptors (nAChRs) in the superficial layers of PFC are mostly expressed in GABAergic interneurons (Ne), whereas the pyramidal neurons (P) of layer V mouse PFC exhibit fast nAChR currents that are mediated by α7-containing nAChRs. Both human and mouse layer VI pyramidal neurons express α5- and β2-containing nAChRs (α5* and β2* nAChRs). Modified from [149] based on [68,150–153]. (B) In layer II/III of mouse prelimbic cortex, α5-containing nAChRs are expressed by vasoactive intestinal polypeptide (VIP) interneurons, somatostatin (Som) interneurons express α7- and β2-containing nAChRs, whereas parvalbumin (Pv) fast spiking neurons express α7-nAChRs [88,150,151]. α5-containing nAChRs control the VIP-mediated disinhibition via Som interneuron inhibition of pyramidal neurons in layers II/III in prelimbic cortex [68]. (C) The α5SNP, a human polymorphism linked to nicotine addiction and schizophrenia (for details see Box 1), decreases the activity of VIP interneurons. This leads to increased Som interneuron activity, a feature of schizophrenia [68]. (D) Chronic nicotine administration desensitizes β2-containing nAChRs on Som interneurons. As a result, Som inhibition of pyramidal neurons is reduced and the activity is normalized. Modified from [68,154].
PD
A hallmark of PD is the loss of nigrostriatal dopaminergic neurons. Presynaptic and postsynaptic nAChRs modulate dopamine release and both in vitro and in vivo animal model studies revealed a crucial role of \(\beta_2\)-containing nAChRs in striatal dopaminergic signaling control [89]. Rodent and monkey PD models exhibit a decrease in the levels of nAChR expression in the striatum, accompanied by dopaminergic degeneration. Specifically, a loss of \(\alpha_6\alpha_4\beta_2\beta_3\) is observed during mild nigrostriatal lesioning, a decrease in \(\alpha_6\beta_2\beta_3\) receptors is seen when the damage is higher, and there are low levels of \(\alpha_4\beta_2\)-containing receptors when the degeneration is extremely severe [89]. Similarly, decreased expression of nAChR is found in the caudate, putamen, and substantia nigra of humans affected by PD and this decrease is linked to the level of nigrostriatal damage [90].

Nicotine is found to reduce levodopa-induced dyskinesias, a major side effect of levodopa therapy, which improves motor abilities in PD patients and protects against nigrostriatal damage [91,92], pointing at nicotine and nicotinic agonists as promising candidates as part of a treatment regimen for PD.

Schizophrenia
Schizophrenia is a neuropsychiatric disorder that is characterized by both positive symptoms (e.g., hallucinations and delusions) and negative ones (e.g., flattened affect) that usually begin in late adolescence or early adulthood [93]. A distinct role of nAChR subunits in schizophrenia has been initially shown by identifying decreased levels of \(\alpha_7\)-nAChRs in postmortem hippocampus [94], cortex [95], and in the thalamus of schizophrenia patients [96]. Also, there is evidence that the expression of \(\alpha_4\beta_2\)-containing nAChRs, as determined by \(^3\)H-nicotine binding, is reduced in the hippocampus of these patients [97].

The prevalence of smoking among schizophrenia patients is three to five times higher than in the general population [98] and schizophrenia patients extract 50% more nicotine per cigarette than other smokers, by inhaling more deeply [39]. The etiology of this prevalence of smoking among schizophrenia patients is not yet understood and several mechanisms have been suggested. Among them, it has been proposed that nicotine serves as a form of self-medication to alleviate the negative symptoms of the disease, enhance cognitive deficits, or reduce the side effects of antipsychotic treatments. At variance with this interpretation, it was suggested that cigarette smoking might be itself a cause of psychosis [100]. Large, longitudinal, prospective studies are needed to investigate the relationship between smoking and psychosis in order to be able to elucidate whether cigarette smoking has a causal role or not in the development of psychosis [101].

Schizophrenia patients develop multiple sensory processing deficits, including auditory sensory processing (P50) impairments, prepulse inhibition (PPI) reductions, and eye-tracking deficiencies [102]. P50 gating impairments have been linked to the chromosome 15q13-14 site of the \(\text{CHRNA7}\) gene [103]. Interestingly, it has been shown that in schizophrenia patients nicotine normalizes the P50 gating deficits and that treatment of mice with \(\alpha_7\)-nAChR agonists corrects the sensory gating anomalies [102,104,105]. Activation of \(\alpha_7\)-nAChRs by nicotine or nicotinic agonists increases glutamate release and, in turn, normalized P50 gating deficits [106]. Moreover, patients with schizophrenia exhibit reduced PPI and eye-tracking deficits, although nicotine intake increases PPI and eye-tracking performance in these patients [107–109]. Finally, studies in animal models, but also in humans, found that nicotine improves cognitive functions such as working memory, attention, and social interactions, which are impaired in schizophrenia patients [104].
In conclusion, clinical trials of nicotinic agonists, but also positive allosteric modulators of defined nAChR oligomers, are of crucial importance to develop potential treatments of psychiatric disorders such as schizophrenia.

**Genetic Studies on the Contribution of nAChR to Human Diseases**

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

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**Box 1. Human Genetic Studies Identify Variants of nAChRs Linked to Major Psychiatric Disorders**

The CHRNA5/CHRNA3/CHRNβ4 Gene Cluster

The 15q25 gene cluster, which contains the CHRNA5/CHRNA3/CHRNβ4 genes, coding for the α5-, α3-, and β4-nAChR subunits, was associated with risk for heavy smoking and nicotine addiction [126–131] and several SNPs were identified [129–132]. The nonsynonymous SNP rs1696968, found in exon 5 of the α5-human gene, involves a substitution of an aspartic acid by an asparagine in position 398 (D398N). The cSNP is present in about 35% of Europeans and 50% of Middle Eastern populations and has been linked to nicotine dependence, lower ratings of aversive effect, delayed smoking cessation, early lung cancer, and cognitive improvement after nicotine intake [126,133]. Recently, the same genetic locus was associated with schizophrenia in a major GWAS study [134]. The cSNP is linked to schizophrenia in both Caucasian and African-American patients and is associated with decreased intrinsic resting functional connectivity in humans [118] (see Figure 3 in main text). Mice with this polymorphism exhibit schizophrenia-related cognitive deficits and hypofrontality that is reversed after chronic nicotine administration [68]. In addition to nicotine dependence and schizophrenia, the 15q25 gene cluster has been associated with alcohol, cocaine, and opioid dependence, suggesting a potential association with substance use disorders in general [127]. However, the same rs1696968_cSNP has been linked to lower prevalence of cocaine use disorder in humans [127].

Interestingly, rare (~5%) missense variants at conserved sites in CHRNβ4 are associated with decreased risk of developing nicotine dependence and decrease the number of cigarettes consumed daily by smokers [135].

The Human CHRNA7 and CHRFAM7A Genes

The human CHRNA7 gene has ten exons and is located on the long arm of chromosome 15q13-q14, which is a highly unstable area of the human genome that is linked to schizophrenia. A polymorphism in the 50-regulatory region (not duplicated) of CHRNA7 (rs3087454) was found to be strongly associated with schizophrenia [136,137]. However, there is no convincing evidence associating the CHRNA7 gene with smoking [138–140].

In humans, gene duplication in exons 5–10 in CHRNA7 during evolution produced a hybrid gene, CHRFAM7A. The duplication is human specific, found neither in primates nor in rodents, but a similar sequence has been identified in gorillas [141]. Its product, referred to as dupa7, lacks part of the N terminal extracellular ligand-binding domain and it is linked to many neuropsychiatric conditions. Dupa7 is considered a dominant-negative regulator of ion channel function [142]. It was suggested that increased expression of the CHRFAM7A gene in patients with schizophrenia might contribute to failure to regulate nicotine binding to high affinity nicotinic receptors. In addition, a 2-bp deletion was identified in exon 6 of the CHRFAM7A gene [143]. This deletion is more common in Caucasians than African-Americans and is a more potent negative regulator of α7-nAChR function than the normal copy and it was linked to both bipolar disorder and schizophrenia [142].

The CHRFAM7A gene can vary in copy number with individuals with one copy or none and deletions of the CHRNA7 and CHRFAM7A are strongly associated with schizophrenia [144,145]. In addition, rare deletions and duplication of the same area have been linked to autism, epilepsy, bipolar disorder, and attention deficit hyperactivity disorder [146]. A recent study that used induced pluripotent cells and neural progenitor cells derived from individuals with heterozygous 15q13.3 deletions and duplications demonstrated that calcium signal cascades that are dependent on α7-nAChRs are downregulated, suggesting that individuals with deletions and duplications of 15q13.3 exhibit cognitive deficits [147].

The CHRNA2, CHRNA4, and CHRNA2 Genes

Missense mutations or indels in CHRNA2, CHRNA4, and CHRNA2 genes have been linked to autosomal dominant nocturnal frontal lobe seizures, which usually occur during non-rapid eye movement sleep [148].
Loss of Control in Nicotine Addiction

Subjects addicted to drugs such as nicotine or cocaine reveal neural circuit impairments associated with disruptions of the dopaminergic system [110]. Drug addiction causes a marked dysregulation of brain circuits involved in reward, motivation, memory, judgment, and self-awareness, including circuits in frontal cortical regions. These deficits cause a compulsive self-administration of drug with a loss of control (altered inhibition) and disrupted cognitive operations that impair judgment and favor relapse [5,110,111]. Behavioral differences and increased dopamine release in response to nicotine leads to greater likelihood of addiction occurring in adolescents compared with adults and long-lasting dysregulation of attention and sensory processing [112,113]. Several molecular changes are taking place as a consequence of chronic nicotine exposure, such as upregulation of α7-nAChRs, increased presynaptic α7-nAChR transmission, upregulation of β2-nAChRs, presynaptic downregulation of β2-nAChRs, and increased dopaminergic neuron activity [5]. An effect of nicotine and ACh on axon excitability was also described, indicating that nAChRs are probably located at nodes of Ranvier in particular along myelinated thalamocortical axons [114,115], revealing a nonsynaptic action of nicotinic agents. Human individuals addicted to nicotine exhibit cognitive deficits similar to those of patients with an impaired ventromedial prefrontal cortex [116].

Functional MRI studies in rodents have shown that, consistent with the enhancing effect of nicotine, acute injections of nicotine increased the activation of prelimbic, frontal motor, and somatosensory cortices as well as the nucleus accumbens, ventral tegmental area, substantia nigra, and thalamus [117]. Chronic administration of nicotine produces pyramidal cell hyperactivity in the prefrontal cortex of awake mice [68]. Moreover, mice expressing a human polymorphism in the α5-nicotinic subunit (rs16969968_α5SNP), which is associated with nicotine addiction and schizophrenia, exhibit reduced pyramidal cell activity in layer II/III of prelimbic cortex compared with wild type control mice due to alterations in the balance between excitation and inhibition [68] (Figure 2C). Interestingly, chronic administration of nicotine through an osmotic minipump was able to restore the hypofrontality associated with the α5SNP, suggesting an explanation of why individuals with schizophrenia may use tobacco smoking as a form of self-medication [68] (Figure 2D). Similarly, humans with the α5SNP exhibit reduced resting state functional connectivity and altered prefrontal cortex circuitry [118] (Figure 3 and Box 1).

Neuroimaging techniques reveal that in smokers, α4β2-containing nAChRs are upregulated compared with nonsmoking individuals. Furthermore, abstinence for 3 to 12 weeks can normalize the receptor levels to that of nonsmokers [119,120]. Yet the possible relationship of these changes to long-term loss of inhibitory control is still not understood.

Tobacco smoking is robustly linked to DNA epigenetic modifications. In smokers, DNA methylation changes take place at several genomic loci, mainly at cytosine-phosphate-guanine sites [121,122]. At most of the loci, smoking causes loss of methylation to the extent that epigenome profiling of DNA methylation patterns associated with tobacco smoking can serve as molecular biomarkers for major diseases such as lung cancer [123]. Exposure to nicotine during prenatal and early postnatal periods is claimed to cause abnormal development of the brain and favors the onset of mental disorders [124]. This is of particular importance, since in some countries, up to about 10% of women smoke during pregnancy, thereby exposing their offspring to nicotine during critical neurodevelopmental periods [124]. Early nicotine exposure produces long-lasting impairments in neuronal plasticity, such as increased spine density and branching in the frontal, medial, and caudal cerebral cortex [125]. Recently, it was demonstrated that activation of heteropentameric nAChRs by early nicotine exposure causes alterations in histone methylation.
in the cerebral cortex, which in turn increases the expression of genes involved in synapse maintenance and dendritic remodeling, together with behavioral alterations such as hypersensitive passive avoidance performance [125].
These studies reveal a dual action of nicotine as a drug; a positive, therapeutic role as a cognitive stimulant and a negative effect as an addictive drug causing loss of control in drug consumption and other cognitive impairments.

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

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

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