

ENS - PSL, UNIVERSITÉ DE PARIS, EHESS

MASTER'S THESIS

A computational approach to nicotinic modulation of working memory and related pathologies

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Declaration of Authorship

I, Elias EL OTMANI, declare that this thesis titled, "A computational approach to nicotinic modulation of working memory and related pathologies" and the work presented in it are my own. Literature reviews, computational simulations, mathematical and computational results analysis, including figures, novel ideas and model extension, and writing of the thesis, are entirely my own work. Computational implementation of the initial model partly used code from Thomas Fontaine, the rest is entirely my own work. Project set-up, regular help and review of the thesis was provided by Dr. Boris Gutkin. I confirm that :

- This work was done wholly while in candidature for the Master of Cognitive Science of this University.
- No part of this thesis has previously been submitted for a degree or any other qualification.
- Where I have consulted the published work of others, this is always clearly attributed.
- Where I have quoted from the work of others, the source is always given.
- I have acknowledged all main sources of help.

Declaration of Novelty

Many work has already focused on computational modeling of working memory. Likewise, modelling of prefrontal dynamics generated by a hierarchy of interneuron subtypes has been performed by my host team and forms the roots of the present work. The latter is original first in that it combines the modelling of distinct interneurons in the context of working memory, which to my knowledge has never been performed using the three interneuronal populations. Moreover, we enriched the model with features such as short-term plasticity dynamics.

Second, and most importantly, there appears to be a gap in the litterature regarding the circuit mechanisms linking molecular data and cholinergic release modalities in the prefrontal nicotinic system to their well studied corresponding cognitive consequences. Indeed, the previously proposed theories are very sparse and carry important drawbacks, as will be further discussed in this work, and to my knowledge no published paper has ever explicitly confronted them.

To start filling this gap, we therefore had to carry out a novel combined litterature review of prefrontal neural circuitry and corresponding nicotinic dynamics. Combined with computational modelling, this allowed us to propose a new unified theory of the network mechanisms through which prefrontal nicotinic acetylcholine receptors modulate cognition, and to formulate testable predictions.

Pre-Registration

This work was initially pre-registered on January 2021. Nevertheless, the predictions, methods, and even precise goal of the present thesis do not follow those stated in the pre-registration, for various reasons :

- As stated in the Methods section, we modified the model in several ways, in order to solve previously undetected mathematical drawbacks and biological realism issues, as well as to bring new biological features. Therefore, we did not go for the conservative parameter adjustments as initially planned.
- The scientific background of the thesis being extremely wide (cellular biophysical properties and wiring rules of the neural circuitry, nicotinic receptors' molecular properties and cognitive roles, clinical phenotypes of several pathologies, machine learning methods for parameter fitting...), most of the literature review couldn't be carried out before the pre-registration. Keeping on with the rest of the review afterwards revealed many unforeseen contradictions, ideas, and questions left to answer, leading to a complete change of paradigm of this project.
- As a consequence of the two above mentioned points, the rationale of the project moved from thorough and circumscribed empirical data-based biological modelling to a wider theoretical study of the general mechanisms of nicotinic neuromodulation of cognition. As in most theoretical works, the observations detailed here are not meant to constitute robust and statistically significant biological findings, but rather proofs of concepts for a mechanistic theory, which will need to be empirically tested.

The original preregistration can however be found [here](#). Suggested reviewers are mentioned at the bottom of the document.

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Abstract

Ecole Normale Supérieure
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Master of Cognitive Science

A computational approach to nicotinic modulation of working memory and related pathologies

by Elias EL OTMANI

Nicotinic neuromodulation of the prefrontal cortex has long been known to be key to cognitive processes such as attention and working memory, and more recent data unravels the distinct roles of different nicotinic acetylcholine receptor subtypes as well as those of tonic and phasic modes of cholinergic release. However, how these features underpin network activity to determine cognition is not known, and a mechanistic explanation of nicotinic pathophysiology is therefore lacking. In the present work we review theories of nicotinic modulation of prefrontal persistent spiking processes, while testing them on a computational model of supragranular microcircuitry. Our simulations match the majority of the empirical findings we proposed to reproduce, and further suggest opposite and complementary roles of tonic and phasic modes of cholinergic release on the stability of WM representations. Moreover, our framework accounts for some of the clinical phenotypes of nicotinic alterations, and provides a mechanistic basis for the self-medication hypothesis of heavy smoking in schizophrenia.

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Going through the successive lock-downs and obstacles while carrying out this research project has not been an easy thing. I would therefore like to thank my advisor, Pr. Boris Gutkin, for finding the tight balance between providing regular and insightful advice, and letting room for autonomous thinking and time for explorations and going past mistakes.

I couldn't have kept the strong motivation to carry out this work if it wasn't for the warm and welcoming environment of my host team, even in times of confinement, through meetings, journal clubs and virtual coffees. Thus, I wish to truly thank all the members of the Group for Neural Theory, including my co-interns, and address very special thanks to Thomas Fontaine, who kindly helped me through my first steps in the project.

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Chapter 1

Introduction & theoretical framework

1.1 Prefrontal neuroanatomy

The prefrontal cortex (PFC) corresponds to the most anterior part of the brain, and is classically divided in primates into a ventral, medial (mPFC) and dorsolateral (dlPFC) part. It is thought to subserve executive functions, complex valuation and decision making, as well as planning and social interactions, and as such is implicated in the vast majority of psychiatric and neurocognitive human disorders. Throughout evolution, this region has undergone tremendous development in primates, rendering interspecies comparisons difficult. Links can be drawn however, as for example the primate dlPFC is thought to have its functional equivalent in the rodent prelimbic cortex (PrLC) (Uylings, Groenewegen, and Kolb, 2003), embedded in the mPFC. Notably, both regions are each species' most well-known substrates of working memory (WM), a fundamental capacity upon which the above higher order processes depend.

The primate PFC displays a neocortical neuroanatomy : neuronal somas are arranged following at least six distinct layers, ranging from the superficial layer I (L1) to the deepest layer VI. The rough interlaminar connectivity is the following : inputs from subcortical regions synapse on layer IV (the 'granular layer'), activating feed-forward projections to layers II and III (L23). The latter integrate this vertical input as well as horizontal ones from other cortical areas, and projects to the deepest layers V and VI, which constitute the cortical output layers to subcortical structures (Harris and Shepherd, 2015). The function of L1 is less clear, it is nevertheless known to receive excitatory thalamic feedback and to project inhibitory connexions to L23. An important difference in rodent PFC is the apparent lack of granular layer : subcortical input project directly to L23 (Uylings, Groenewegen, and Kolb, 2003). Regarding horizontal organization, many neocortical areas are constituted of cortical columns, which stand for vertical units comprising neurons sharing a given function or stimulus sensitivity. Although the columnar organization of the PFC is still under debate, we shall use here the term "column" to refer to a region of short horizontal radius (~50 micrometers). As our work focuses on supragranular layers, we will now detail their intralaminar neurohistology.

The majority (85-90% in rodents) of neocortical neurons are glutamatergic "pyramidal neurons" (PYR). They strongly excite the remaining 10-15% which corresponds to GABAergic inhibitory interneurons (INs), and which display a discouraging variety of morphological, pharmacological, biophysical and ultimately functional profiles. Over the last decade however, great advances have been made on their classification, unraveling three major subpopulations identified by their mostly non-overlapping expression of parvalbumin (PV), somatostatin (SOM) or serotonin (5HT3)

markers and accounting for more than 95% of INs. This pharmacological classification also corresponds to a myriad of functional differences, of which numerous are of relevance to our modeling work. Unless stated otherwise, the informations below are drawn from Tremblay, Lee, and Rudy, 2016.

PV neurons are the largest population across the neocortex, but appear to be four to five times fewer than SOM and VIP neurons in mPFC supragranular layers (Kim et al., 2017; Anastasiades and Carter, 2021). Their output connectivity profile is surprisingly simple : they target almost exclusively perisomatic regions of PYR neurons (thereby exerting powerful shunting inhibition) and themselves. Projecting horizontally their wide axonal and dendritic arbors and being electrically connected to each other, they form a large synchronized population which non specifically inhibits all local PYR neurons (Fukuda et al., 2006; Fino, Packer, and Yuste, 2013), and moreover their connexion probability with PYR neurons barely decreases over short distances (Holmgren et al., 2003), contrary to other INs (Jiang et al., 2015). These characteristics, along with their low target-dependency as opposed to SOM neurons described below (Table 1.1), motivates the choice in the second part of this work to consider only one single PV population even when modeling competition between two cortical columns. Because their biophysical properties give them very fast kinetics, PV neurons are able to quickly react to inputs, exerting synchronized shunting inhibition, allowing neural oscillations and coincidence detection. This latter function is particularly well illustrated by their embedding in the “feedforward inhibition” circuit motif : local or distal excitatory inputs such as thalamic signals almost systematically project both onto PYR cells (monosynaptic excitation) and PV neurons - the latter ultimately consists in disynaptic inhibition of PYR neurons, leaving only a couple of milliseconds for the monosynaptic excitation to trigger an action potential before PV inputs shut activation off. PYR neurons will therefore fire only if they receive synchronized suprathreshold input from their different afferents during this short time window. Excitatory synapses onto PVs and inhibitory PV outputs however are strongly depressing - feedforward inhibition rapidly weakens for sustained inputs, allowing pyramidal excitation.

SOM neurons represent the largest population of mPFC interneurons (Kim et al., 2017; Anastasiades and Carter, 2021). Their output connectivity in supragranular layers is also quite simple : they uniformly inhibit every other neural population but themselves. Although their dendritic targeting of PYR neurons leads to a weaker inhibition of PYR cells, excitatory synapses onto SOM are strongly facilitating, allowing these neurons to keep up with the most active local PYR neurons, providing supralinear negative feedback to them (Kapfer et al., 2007; Yavorska and Wehr, 2016) (effectively preventing runaway excitation) but also to neighboring less active neurons, mediating intra- and intercolumnar lateral inhibition (Kätsel et al., 2011; Roux and Buzsáki, 2015) and winner-takes-all mechanisms. Importantly, they receive mostly horizontal rather than translaminar inputs as opposed to PV (Yavorska and Wehr, 2016).

The last population, 5HT3+ neurons, is by far the most heterogeneous one. A large portion of them however (40%) expresses the vaso-intestinal polypeptide (VIP) and can be to a certain extent identified as a single functional population. VIP cells project to upper and deeper layers but are largely intracolumnar, displaying a very local horizontal action contrary to the other populations. Interestingly, their principal targets are SOM and to a lesser extent PV neurons, thereby disinhibiting PYR neurons. See Figure 2.2-A for the complete wiring diagram. The remaining 5HT3+ cells notably comprise neurogliaform cells (NGFC), which provide slow and long lasting volume inhibition to all populations (Pfeffer et al., 2013).

1.2 Ultra-slow oscillations and working memory

Working memory (WM) is defined as the ability to retain information on-line over short delays, for and until subsequent use. This ability is fundamental for the more complex PFC functions mentioned earlier. WM is widely measured through the delayed match-to-sample task (DMTS) : an animal is presented with a sensory cue before the visual scene is hidden during the “delay” period, after which the animal has to recall the information carried by the cue, e.g its location or type. A failure of the task (i.e an incorrect response at the last phase) can correspond to either encoding, retention or recalling errors. A detection (or “encoding”) error corresponds to the stimulus not being properly loaded in WM at the “cue” phase, it is thus independent of the delay’s length and is thought of as a consequence of attentional deficits. A retention (or “maintenance”) error on the other hand corresponds to the information being forgotten during the delay period, and therefore depends on its length. Additionally during the delay, irrelevant cues can be presented in order to assess the sensitivity of retention errors to distractors. See Figure 2.2-(B,C,D) for examples of DMTS simulations and corresponding errors.

The precise neurophysiology of WM is not yet fully understood, partly because the concept itself is rather generic and doesn’t stand for a single specific mechanism, as suggested by its all-encompassing definition. However, the role of persistent local neural activity in the PFC has been particularly acknowledged : after cue presentation in the DMTS, stimulus-specific neurons (“delay cells”) exhibit and maintain high firing rates throughout the delay, allegedly supporting the mnemonic retention, before falling back to baseline levels at response time (Goldman-Rakic, 1995; Constantinidis et al., 2018). A popular hypothesis is that this persistent activity stems from local recurrent connexions between PYR neurons, although larger (inter-areal loops) and lower (voltage fluctuations, synaptic short-term plasticity or STP) scale dynamics are also likely to play a role (Wang, 2001; Arnsten et al., 2010; Mongillo, Barak, and Tsodyks, 2008).

The temporal scales and amplitudes of this sustained activity resemble those of neocortical transitions between “UP” and “DOWN” states (Rooy et al., 2021) electrophysiologically recorded in animal models and cortical slices, whereby all neural types display locally synchronized voltage and firing rate fluctuations which either spontaneously involve large neural populations and propagate through the cortex as in slow-wave sleep or quiet wakefulness (Sanchez-Vives and McCormick, 2000; Wester and Contreras, 2012), or entail sparse and clustered neural ensembles in stimulus-triggered “cortical flashes”, reminiscent of WM mechanisms (Cossart, Aronov, and Yuste, 2003). Interestingly, EEG spontaneous “ultra-slow fluctuations” (USFs, < 1Hz) can also be observed in the so-called Default Mode Network in humans (Moutard, Dehaene, and Malach, 2015), and the bridge with the aforementioned oscillations constitutes a tempting hypothesis (Koukouli et al., 2016). Besides WM, several other roles for these fluctuations have been proposed, ranging from cellular regeneration (Vyazovskiy and Harris, 2013) to migration and consolidation of mnemonic representations (Staresina et al., 2015). In any case, they strongly suggest that dynamic bistability and attractor networks are a general feature of the neocortex (Cossart, Aronov, and Yuste, 2003). Importantly for our modelling framework, STP mechanisms are thought to bear strong significance both in USFs and WM (Fanselow, Richardson, and Connors, 2008; Krishnamurthy, Silberberg, and Lansner, 2012).

1.3 Nicotinic neuromodulation

Every known neuromodulator plays a role in PFC function, but the scope of our work is restricted to nicotinic modulation. From the functional point of view, acetylcholine in the brain is thought of as generally increasing signal-to-noise ratio and thalamocortical processing, reducing corticocortical effective connectivity. Cholinergic innervation of the PFC comes mostly from basal forebrain nuclei (Dani and Bertrand, 2007) and acts, through a complex interplay of tonic and phasic release as well as synaptic and volume transmission (Bloem, Poorthuis, and Mansvelder, 2014), on muscarinic and nicotinic acetylcholine receptors (nAChRs). nAChRs are excitatory cationic channel receptors composed out of five subunits, and owe their name to their ability to bind nicotine as an exogenous agonist. Different subunit combinations yield different receptors, the two most frequent in the PFC being the heteropentameric $\alpha 4\beta 2^*$ receptor, which is built out of two ligand-binding $\alpha 4$ and two accessory $\beta 2$ subunits (the asterisk denoting the unspecified fifth subunit), and the homopentameric $\alpha 7$ receptor (composed of five $\alpha 7$ subunits) (Gotti and Clementi, 2004). Whereas the latter display a low affinity to ACh, $\alpha 4\beta 2^*$ receptors are way more responsive both to ACh and to nicotine. However, although ACh provokes a desensitization over the course of hundreds of milliseconds (Auerbach and Akk, 1998), nicotine-mediated desensitization unfolds way faster and, therefore, nicotine virtually behaves as an antagonist over the timescales considered in this work (Poorthuis et al., 2012; Koukouli et al., 2017). The presence of the $\alpha 5$ subunit in the $\alpha 4\beta 2^*$ receptor increases its sensitivity and time opened in response to agonists, and to a certain extent protects the receptor from desensitization (Bloem, Poorthuis, and Mansvelder, 2014).

In rodents, significant nAChR expression from PYR cells only occurs in subgranular layers - in L23, nAChRs are solely expressed by INs (Poorthuis et al., 2012; Hedrick and Waters, 2015). Homopentameric $\alpha 7$ receptors are found in both PV and SOM populations, whereas $\alpha 4\beta 2^*$ receptors are displayed in SOM and VIP neurons (Bloem, Poorthuis, and Mansvelder, 2014). Only in the latter can they form the $\alpha 4\alpha 5\beta 2$ subtype (Porter et al., 1999, see also Figure 2.2-A). PV neurons are rather unresponsive to nicotinic stimulation, their excitation through their low-affinity $\alpha 7$ receptors being most likely countered by their inhibition through VIP and SOM $\alpha 4\beta 2^*$ -mediated activation.

The resulting effect of nicotinic stimulation of L23 on PYR firing rates is not so clear cut, as to our knowledge it hasn't been explicitly studied under which conditions, if not all, direct nicotinic excitation of SOM neurons exceeds their indirect inhibition through nicotinic excitation of VIP neurons. However, Poorthuis et al., 2012 point towards an effect of overall decrease of PYR mean firing rates, a statement that is consistent with the hyperfrontality of $\beta 2$ -KO mice in Koukouli et al., 2017, as both populations' main nicotinic receptors critically depend on this subunit.

The critical role of cholinergic modulation in WM and attention has been known for decades, and lately the function of distinct nAChRs in the PFC has been brought to light (see Table 1.1). Prefrontal $\alpha 4\beta 2$ receptors foster resistance to distractors (Sun et al., 2017). This is consistent with the role of their principal expressor in L23, SOM neurons, in surround inhibition and winner-takes-all mechanisms. The same receptors are also permissive for attention in mice (Guillem et al., 2011; Parikh et al., 2010), consistent with the finding that they fully account for the amplitude of the 1-second-long medial prefrontal cholinergic transients allowing cue detection in the sustained attention task (Parikh et al., 2007; Parikh et al., 2008). These transients seem to be triggered only by cues involving a reorientation of attention or a change of strategy

in the sustained attention task, and a failure of the cue to elicit them predicts that it will be missed.

Although as we just stated, they are well characterized both at the molecular and cognitive levels, the intermediate circuit mechanism hasn't yet been explored and will be one of the main focuses of our work. We found two distinct theories in the literature : Bloem, Poorthuis, and Mansvelder, 2014 state that since nicotinic stimulation of L2/3 results in a general increase of the inhibitory tone, "nAChR stimulation would 'reset' the network so that new incoming information can be processed". This is supported by the above-mentioned evidence in favor of a nicotinic PYR inhibition (Arroyo, Bennett, and Hestrin, 2014; Poorthuis et al., 2012; Obermayer et al., 2018). Conversely, we can read in Kamigaki, 2019's review the hypothesis that "cholinergic projections in the PFC preferentially recruit VIP neurons and thereby enhance task-relevant signals", which is supported by Porter et al., 1999 showing selective recruitment of VIP neurons by nicotinic agonists, and consistent with the general view of cholinergic modulation as increasing the signal-to-noise ratio and thalamocortical processing. The molecular properties of the VIP-specific $\alpha 4\alpha 5\beta 2$ receptor (higher sensitivity to ACh, longer time opened when it binds its agonist) seem to point in the same direction.

However, both theories carry some caveats : on the one hand, Bloem's theory of network reset seems inconsistent with the duration of the transient, which lasts for one to several seconds and would therefore prevent the encoding of the incoming information. In order to save the theory, we can nevertheless resort to the desensitization effect that high concentrations of ACh have on the $\alpha 4\beta 2^*$ (but not the $\alpha 4\alpha 5\beta 2$) receptor, an ad-hoc explanation which would signify that the actual SOM-mediated network-resetting effect only takes place during the earliest portions of the transient, the rest consisting in $\alpha 4\alpha 5\beta 2$ -mediated VIP activation. On the other hand, Kamigaki's theory lacks empirical support, as the references given for preferential recruitment of VIP neurons weren't actually about the PFC (crucially Porter et al., 1999's observations were carried out in the motor cortex), and nicotinic canonical circuits don't seem to be homogeneous across the cortex. The hypothesis seems furthermore incompatible with the arguments we mentioned above regarding PYR's inhibition being the dominant effect of nicotinic modulation. Yet, one interesting possibility makes the theory conceivable, and it resides in the electrophysiological and circuit properties pointed out in Chen, Sugihara, and Sur, 2015. They found that, in the visual cortex, nicotinic stimulation strongly recruits SOM neurons at concentrations as low as $1 \mu M$, thought to be due to their low-threshold spiking properties, whereas VIP neurons only start firing at concentrations of 10 mM , possibly secondary to inhibition from SOM neurons at lower concentrations, and despite VIP's $\alpha 4\alpha 5\beta 2$ receptor having higher affinity to ACh. Because these circuits and electrophysiological specificities are found everywhere across the cortex, one could imagine that the sustained, trial-related cholinergic tone corresponds to concentrations recruiting SOM neurons, thereby stabilizing the content of working memory against distractors, whereas phasic transients would reach concentrations corresponding to VIP neurons' activation and increase in thalamocortical processing. A phenomenon that will be of importance later on to study these theories is current rectification : nicotinic currents are larger in neurons which are less depolarized (Dani and Bertrand, 2007).

$\alpha 7R$ have also been shown to play a key role in delay-related activity, as their stimulation in primates at very low doses improves WM (Castner et al., 2011) and sharpens the spatial tuning of delay cells (Yang et al., 2013), an effect that inverts at

higher doses. However, an important quandary arises, as this role has been hypothesized to be due to facilitation of L23 pyramidal recurrent connexions via postsynaptic $\alpha 7R$ expression, an explanation that is inconsistent with the lack of nAChRs expression by L23 PYR cells as pointed out by Poorthuis et al., 2012. As the latter study was performed in rodents, it is likely that that $\alpha 7R$ expression patterns are different in primates (Yang et al., 2013), consistent with the lack of evidence of any beneficial effect of $\alpha 7$ receptor agonists in rodents and even better performance in presence of specific antagonists or genetic deletions (Howe et al., 2010).

1.4 Associated pathologies

Two conditions associating prefrontal, working memory and nicotinic impairments are schizophrenia (SCZ) and Alzheimer's disease (AD), both caused by a combination of genetic and environmental factors. SCZ is a frequent psychiatric illness which often declares in late adolescence and which encompasses both "positive" (hallucinations, delusions) and "negative" (cognitive impairments, alogia, avolition, flat affect...) symptoms, as well as disorganized speech and behavior (Lewis, Hashimoto, and Volk, 2005). AD on the other hand is a late-onset neurodegenerative disorder which leads to progressive loss of episodic memory and to more general cognitive impairments, representing the first cause of dementia worldwide (Mucke, 2009). Its early clinical presentation is called Mild Cognitive Impairment (MCI).

WM represents a supramodal (Park and Holzman, 1992; Lee and Park, 2005) core deficit in SCZ (Lewis, Hashimoto, and Volk, 2005; Forbes et al., 2009), which seems to be mostly secondary to encoding errors (Lee and Park, 2005; Hartman et al., 2003; Gold et al., 2010) despite intact attentional control (Gold et al., 2006), although a sensitivity to distractors is also documented (Park and Holzman, 1992; Jazbec et al., 2007; Smucny et al., 2013). Conversely, WM deficits in MCI and AD seem to be strongly delay-dependent (Sahakian et al., 1988; Belleville et al., 2008; Gagnon and Belleville, 2011), and also sensitive to distractors (Gagnon and Belleville, 2011; Berger et al., 2015).

The pathophysiology of SCZ is poorly understood, although much evidence points towards a hypofunction and lower resting-state activity of the dlPFC (Hill et al., 2004). Multiple theories have been developed, but a common pathophysiological pattern seems to involve insufficiency in PFC recurrent activity, triggering a compensatory hypofunction of PV (Lee and Park, 2005) and SOM (Dienel and Lewis, 2019) populations in supragranular layers. We also see decreased prefrontal expression levels of $\alpha 7R$ (Guan et al., 1999; Gotti and Clementi, 2004) and, most importantly, a strong association with a single nucleotide polymorphism of the CHRNA5 gene ($\alpha 5SNP$), coding for the $\alpha 5$ nicotinic subunit (Psychiatric Genomics Consortium, 2014). The latter mutation concerns more than a third of European population, it figures among the best predictors of tobacco addiction (Tobacco and Consortium, 2010), a major comorbidity of SCZ, and is associated with WM (Winterer et al., 2010; Di Giorgio et al., 2014) alterations even in healthy individuals. There is therefore a strong association between the nicotinic system and SCZ, and the high prevalence of nicotine addiction among the patients could be a form of self-medication, given the compensatory effects of nicotine (Koukouli et al., 2017). Alternative theories include a possible causal role of tobacco on psychosis onset (Gurillo et al., 2015), or simply a larger vulnerability to addictions caused by a cognitive control deficit, in which case the specificity of nicotine addiction over other substances remains puzzling.

AD's pathological process is to a certain extent better understood, as the role of neocortical, hippocampal and thalamic accumulation of harmful peptides in progressive neural death and loss of cholinergic tone is now well established (Mucke, 2009). The β -amyloid ($A\beta$) peptide plays a prominent role, and has been found to inhibit $\alpha 7$ nAChRs even at picomolar concentrations, which might explain WM impairments and (by contrast to SCZ) prefrontal hyperactivity in MCI, a stage prior to any cholinergic depletion and pathological neural death (Lombardo and Maskos, 2015; Koukouli, Rooy, and Maskos, 2016).

1.5 Rationale

Collaborative work including my host team (Koukouli, Rooy, and Maskos, 2016; Koukouli et al., 2017) identified disruptions of prefrontal USFs in animal models of SCZ and MCI, i.e. mice expressing the human $\alpha 5$ SNP and $A\beta$, respectively. Computational modelling proposed a mechanistic explanation of these disruptions, and suggested they could have important implications for WM impairments (Rooy et al., 2021). The objective of the present study is to propose a theory of nicotinic modulation of WM, to further investigate the possible mechanisms through which the $\alpha 5$ SNP might undermine cognition (and specifically cue detection), and to a lesser extent those of other discussed nicotinic alterations such as the $\alpha 7$ hypothesis of MCI, the effect of nicotine exposure or the observed general cholinergic depletion of declared AD.

To do so, we will first analyze the behavior of the simple model and see how it fits with the data below, before confronting a two-populations model to the findings regarding resistance against distractors, one population responding to a distractor occurring during the delay period. We will then consider a situation in which the irrelevant population is already active when the rewarding stimulus must be detected, evaluating the possible ways (according to Bloem's or Kamigaki's hypothesis) through which the cue-triggered nicotinic transient could facilitate the attentional switch, and whether our simulations' results suggest that this mechanism might be implicated in the pathophysiology of the $\alpha 5$ SNP and in its possible remediation by nicotine. On the basis of the articles listed in Table 1.1, and leaving aside data from primates because of the discrepancies regarding the role of $\alpha 7$ receptors, we will consider that before jumping to predictions, our model should first reproduce the following findings :

- VIP facilitation should enhance WM performance
- VIP inhibition (as in $\alpha 5$ SNP) should reduce P(detection) and thus WM performance
- PV facilitation should impair WM
- PV inhibition should impair WM
- SOM inhibition (as during nicotine exposure) should worsen sensitivity to distractors and enhance WM in the $\alpha 5$ SNP condition
- SOM facilitation should impair working memory in no-distractor conditions but increase resistance against distractors otherwise

TABLE 1.1: Literature review of cellular and nicotinic determinants of WM (1). NB : Papers marked with a (*) are specifically carried out in mice PFC, and therefore bear significant importance in our modelling framework

Neural population or nAChR subunit	Reference	Methods	Results
All	Rao, Williams, and Goldman-Rakic, 2000	Monkey, dlPFC, BMI (GABA blocker) infusion	Loss of spatial tuning
PV	Lagler et al., 2016 (*)	Mice, PrLC, WM in maze navigation	Heterogeneous recruitment of PVs during delay (episode-dependent).
	Rao, Williams, and Goldman-Rakic, 1999	Monkey dlPFC recordings, DMTS	Strong isodirectional tuning of nearby PYR-PVs pairs, mostly stemming from shared inputs.
	Murray et al., 2015 (*)	Mice, PFC, WM in maze navigation.	PV blocking leads to WM deficit (attributed to disruption of oscillations).
	Ferguson and Gao, 2018	Review	Increasing or decreasing PV excitability impairs WM
SOM & PV	Kim et al., 2016 (*)	Mice, PFC optogenetic activation, spatial WM	High PV activity during delay but low target-dependency. High target-dependency for SOM. SOM optogenetic stimulation leads to slight but significant WM impairment
	Abbas et al., 2018 (*)	Mice, PFC optogenetic inhibition, WM in maze navigation	SOM inhibition during encoding perturbs WM (role in long-range input coordination), PV doesn't. SOM inhibition also disrupts the tuning for the preferred arm, PV doesn't.
SOM	Wang et al., 2004	DMTS modelling	Mediate resistance against distractors (empirically, inverted tuning curves with respect to nearby PYR)

TABLE 1.2: Literature review of cellular and nicotinic determinants of WM (2)

Neural population or nAChR subunit	Reference	Methods	Results
SOM & VIP ($\beta 2$)	Kamigaki and Dan, 2017 (*)	Mice, delayed Go / No-Go task, optogenetics	VIP activity enhances WM, SOM activation impairs it
	Guillem et al., 2011 (*)	$\beta 2$ -KO mice, attentional task (choice reaction time).	Strong attentional impairment, reversed by lentiviral $\beta 2$ re-expression in PrLC.
	Sun et al., 2017	Monkey dlPFC, selective $\beta 2$ agonist or antagonist	Agonist : No enhancement of the delay firing, but improved resistance against distractors. Antagonist : No impact on delay activity but reduction in fixation cells firing.
	Parikh et al., 2010 (*)	Recording of glut. & ACh transients in layers III & V of mice PrLC, attentional task	$\beta 2$ receptors fully account for the amplitude of the 1-second-long cholinergic transients necessary for cue detection.
	Howe et al., 2010	Mice, sustained attention task, systemic nicotine or selective $\alpha 4\beta 2*$ agonist	The $\alpha 4\beta 2*$ selective agonist increases detection when attentional reorientation is involved.
Nicotine	Howe et al., 2010	See above	Nicotine alone either doesn't affect or reduces detections.
	Mirza and Stolerman, 1998	Mice, sustained attention task, systemic nicotine administration	Attentional improvement only under certain conditions.
	Sacco et al., 2005; Barr et al., 2008; Rezvani and Levin, 2001	Nicotine administration in patients with SCZ and healthy subjects	Systematic WM and attentional enhancement in SCZ. Lesser cognitive enhancement in healthy subjects.
	Lawrence, Ross, and Stein, 2002	Nicotine administration in healthy subjects	No WM enhancement in non-smokers.
	Bailey et al., 2010	$\alpha 5$ KO mice, attentional task (5-choice serial reaction time)	Impairment in performance only under high attentional demands
VIP ($\alpha 5$)	Winterer et al., 2010	Cognitive tests in humans with $\alpha 5$ SNP	Impairment in n-back performance

Chapter 2

Methods

2.1 Model formulation & inference

2.1.1 Original model formulation

The model used to investigate USFs disruptions under nicotinic alterations (Rooy et al., 2021) is an adaptation of the Wilson-Cowan rate model (Wilson and Cowan, 1972). The latter states that the activities of an excitatory (E) and an inhibitory (I) neural populations can be described by :

$$\begin{aligned}\tau_m \frac{dE}{dt} &= -E + (1 - r_E E) S_e (k \omega_{EE} E - \omega_{IE} I + k I_{ext}) \\ \tau_m \frac{dI}{dt} &= -I + (1 - r_I I) S_i (k' \omega_{EI} E - \omega_{II} I + k' I_{ext})\end{aligned}\quad (2.1)$$

Where τ_m is the membrane time constant of the population, r_E and r_I are the population's characteristic refractory periods, E and I are transforms of the proportions of active cells respectively in the excitatory and inhibitory population (e.g. mean firing rates), k and k' are population constants, ω_{xy} represent the weights of the four directed connexions, and S_x stand for the subpopulation response functions, determining the expected proportion of cells in the sensitive subpopulation receiving suprathreshold input. This input is a linear combination of the weighted activities of the excitatory and inhibitory populations, as well as external (I_{ext}) inputs to the population. The model from Rooy et al., 2021 was designed to reproduce the data from Koukouli et al., 2017. As such, it separately considered PYR, PV, SOM and VIP populations' firing rates (r_e , r_p , r_s and r_v respectively) as the four distinct dimensions of our dynamical system. Subpopulation response functions were taken to be sigmoidal functions. Furthermore, the shunting inhibition of PV cells was taken into account such that instead of linearly adding to PYR inputs, a fraction $q = 0.8$ of PV outputs was exerted as divisive, the rest being linear subtractive inhibition. This mixed inhibition was introduced by following Papasavvas et al., 2015 response functions F_x and their corresponding plateau of population activity K_x (see the following section for details). Refractory periods were not considered in the model. Conversely, population linear scaling factors A_x were introduced to facilitate the fitting procedure. Finally, additive gaussian noise $\epsilon(t)$ of variance σ was included, as well as Poisson-distributed excitatory transients of fixed amplitude to PYR neurons, standing for UP-state-triggering subcortical inputs. As a result, the mean firing rate of a population x was described by :

$$\begin{aligned}\tau_m \frac{dr_x}{dt} &= -r_x + (A_x K_x (\frac{q \omega_{px} r_p}{A_p}) - r_x) \\ F_e (\frac{r_e \omega_{ex}}{A_e} + I_{ext-x} + I_{adp}, \frac{\sum_{i=0}^j r_i \omega_{ix}}{A_i} + \frac{(1-q)r_p \omega_{px}}{A_p}, \frac{qr_p \omega_{px}}{A_p}) + \sigma \xi(t)\end{aligned}\quad (2.2)$$

Where I_{ext-x} stands for the external current injected into a population, and $I_{ext-e} = I_{0-e} + I_{trans}$, the last term being the Poisson-distributed excitatory transient. I_{adp} is

the current implementing firing rate adaptation of the PYR population, and follows the following first order dynamics :

$$\tau_{adp} \frac{dI_{adp}}{dt} = -I_{adp} + r_e J_{adp} \quad (2.3)$$

Where J_{adp} is the adaptation strength. Once fitted to the data, the model behaves as a stochastic bistable oscillator alternating between 'UP' and 'DOWN' states.

2.1.2 Model extension

Several modifications and added features were brought to the model for it to better suit the present work. First, after noticing an unexpected excitatory effect of PV neurons during DOWN states, we studied the sigmoidal subpopulation function of Papasavvas et al., 2015 :

$$F_e(x, \theta, \alpha) = \frac{1}{1 + \exp(-\frac{\alpha_j}{1+\alpha}[x - (\theta_j + \theta)])} - \frac{1}{1 + \exp(\frac{\alpha_j \theta_j}{1+\alpha})} \quad (2.4)$$

x represents the excitatory input ("driver") to the population, whereas θ and α respectively stand for the subtractive and divisive input to the population. The effect of the former is to shift the input-output curve along the x axis in the driver-output plane (Figure 2.1-A). Conversely, α reduces the slope or "gain" of the curve, along with decreasing the value of the plateau of maximal response down to :

$$k = \lim_{x \rightarrow \infty} F(x, \theta, \alpha) = \frac{\exp(\frac{\alpha_j \theta_j}{1+\alpha})}{1 + \exp(\frac{\alpha_j \theta_j}{1+\alpha})} \quad (2.5)$$

θ_j and α_j are the corresponding minimal displacement and maximal slope. 2.1-A suggests the excitatory effect of PVs in the model might come from the flattening of the curve in its lower portion. We can explicitly differentiate the response function over α :

$$\frac{dF_e}{d\alpha} = \frac{\alpha_j}{(1+\alpha)^2} \cdot \frac{\theta_j \exp(\frac{\alpha_j \theta_j}{1+\alpha})}{[1 + \exp(\frac{\alpha_j \theta_j}{1+\alpha})]^2} - \frac{(x - \theta_j - \theta) \exp(-\frac{\alpha_j(x - \theta_j - \theta)}{1+\alpha})}{[1 + \exp(-\frac{\alpha_j(x - \theta_j - \theta)}{1+\alpha})]^2} \quad (2.6)$$

Evaluating it at typical input values of DOWN and UP states with original model parameters Figure 2.1-B indeed yields an increasing response function of the divisive inhibition for DOWN states. To correct for this effect we decided to resort to the similar Papasavvas et al., 2020 function, which was developed by the same authors for modeling the same biological phenomenon :

$$F(x, \theta, \alpha) = \left(\frac{\alpha_j}{\alpha_j + \alpha} \right) \cdot \left[\frac{1}{1 + \exp(-\alpha_j[x - (\theta_j + \theta)])} - \frac{1}{1 + \exp(\alpha_j \theta_j)} \right] \quad (2.7)$$

Along with the respective plateau of maximal input :

$$k = \lim_{x \rightarrow \infty} F(x, \theta, \alpha) = \frac{e^{\alpha_{e,i}}}{1 + e^{\alpha_{e,i}}} \cdot \frac{\alpha_{e,i}}{\alpha_{e,i} + \alpha} \quad (2.8)$$

The relatively larger impact on the plateau of maximal input than on the slope provides a workaround to the problem (Figure 2.1-A - bottom right). It is worth noting that we could have kept using Papasavvas et al., 2015's function by changing the

arguments to $F(x/\alpha, \theta, 0)$ (Figure 2.1-A - bottom left), however this “driver divisive” trick omits the lowering of the plateau at maximal input, as at infinity it converges to $K(0)$. Note that we kept the values of α_j and θ_j detailed in Rooy et al., 2021.

Second, since the model aims at reproducing neural traces over timescales of seconds, we chose to incorporate the short term synaptic plasticities described in section 1.1). In order to do so, we incorporate a synaptic efficacy factor D_{xy} , so that the subpopulation response function of a response population y in response to excitatory, subtractive or divisive input populations x now takes as each of its respective inputs :

$$\sum_x^x r_x \omega_{xy} D_{xy} \quad (2.9)$$

Where D_{xy} is either kept constant at a value of 1 for synapses not subject to STP, or evolves between 1 and a second steady-state D_{xy}^{SS} according to :

$$\tau_D \frac{dD_{xy}}{dt} = (c_{xy} - D_{xy}) - r_x (D_{xy} - D_{xy}^{SS}) \quad (2.10)$$

Where the constant c_{xy} is defined such that for typical median firing rates r_x of a population x in the DOWN state (Table 2), D_{xy} maintains a steady-state close to 1 :

$$\tau_D \frac{dD_{xy}}{dt} \Big|_{D=1} = 0 \Rightarrow c_{xy} = r_x (1 - D_{xy}^{SS}) + 1 \quad (2.11)$$

Then as presynaptic firing rates increase, D moves towards D^{SS} , which is set to 0.5 for depressing synapses (PYR to PV, PV to PYR, thalamus to PV) and 1.5 for the facilitating PYR-to-SOM, following Zaitsev and Lewis, 2013’s postsynaptic potentials amplitude ratios. τ_D is set to 10 s.

We also changed the membrane time constant of PV neurons to 7 ms according to Povysheva et al., 2013, reflecting their faster kinematics. Finally, we took into account inputs from subcortical structures to all populations but SOM neurons, according to Tremblay, Lee, and Rudy, 2016. The latter transients were step functions instead of Dirac delta functions, since we manipulated both their amplitude and duration. The complete model is therefore :

$$\left\{ \begin{array}{l} \tau_m \frac{r_e}{dt} = -r_e + (A_e K(k_d r_p \omega_{pe} D_{pe} / A_p) - r_e) \\ \quad F(r_e \omega_{ee} + I_{ext-e} + I_{trans} \omega_{te} + I_{adp}, (1 - k_d) r_p \omega_{pe} D_{pe} + r_s \omega_{se}, k_d r_p \omega_{pe} D_{pe}) + \sigma_e \xi(t), \\ \tau_m^p \frac{r_p}{dt} = -r_p + (A_p K(0) - r_p) F(r_e \omega_{ep} + I_{ext-p} + I_{trans} \omega_{tp} D_{tp}, \sum_{p,s,v}^x r_x \omega_{xp} D_{xp}, 0) + \sigma_p \xi(t), \\ \tau_m \frac{r_s}{dt} = -r_s + (A_s K(0) - r_s) F(r_e \omega_{es} + I_{ext-s}, r_v \omega_{vs}, 0) + \sigma_s \xi(t), \\ \tau_m \frac{r_v}{dt} = -r_v + (A_v K(0) - r_v) F(r_e \omega_{ev} + I_{ext-v} + I_{trans} \omega_{tv}, r_s \omega_{sv}, 0) + \sigma_v \xi(t) \end{array} \right. \quad (2.12)$$

Importantly, in line with the initial model we didn’t take into account SOM-to-PV connexions, the strong influence of PVs in the network leading to undesired disinhibitory effects of SOM neurons.

In line with section 1.4, the α 5SNP is modelled as a reduction in I_{ext-v} , increasing concentrations of nicotine correspond to reductions in I_{ext-s} , the effect of $A\beta$ translate into reductions in both I_{ext-s} and I_{ext-p} , and general cholinergic depletion reduces all external currents but I_{ext-e} . In these two last conditions, PVs’ low responsiveness to nicotine is mediated by reductions in I_{ext-p} five times lower than the concomitant ones.

2.1.3 Inferential procedure

In this section are described some additional modifications brought to the model before attempting parameter inference. Since the latter procedure did not work out, these last changes were not included in the complete model, which is therefore fully detailed in the previous section.

Regular model fitting computes the likelihood function $P_M(\theta|x_0)$, which yields the probability that experimental observations x_0 were generated by a set of parameters θ through our model M . The parameter set yielding the maximal likelihood is then kept. Contrary to the so-called “prescribed” models, “implicit models” such as ours are defined by their analytically intractable likelihood, which often means resorting to techniques of the Simulation-Based Inference framework. The latter is also called Approximate Bayesian Computation (ABC) because, by performing numerous simulations with random parameter sets, it aims at inferring $P_M(\theta|x_0)$ from $P_M(x_0|\theta)$, according to Bayes law :

$$P(\theta|x_0) = \frac{P(x_0|\theta)P(\theta)}{P(x_0)} \quad (2.13)$$

Where $P(\theta)$ corresponds to our prior knowledge about the parameters (e.g, synaptic weights can't be negative). Assuming that different model outputs are a priori equally likely :

$$P(\theta|x_0) \sim P(x_0|\theta)P(\theta) \quad (2.14)$$

Because implicit models often involve stochastic dynamics and continuous high-dimensional output data, it doesn't make sense to fit directly to the raw data x_0 but rather to some corresponding summary statistics S_0 (see the statistics provided in Rooy et al., 2021). Under its simplest formulation, ABC consists in sampling parameter sets from our prior distribution $P(\theta)$, generating synthetic data x' , and keeping or rejecting θ depending on the corresponding summary statistics S' being or not sufficiently close to S_0 :

$$\rho(S', S_0) < \epsilon \quad (2.15)$$

Where ρ is our distance function (e.g, euclidean) and ϵ is our rejection threshold, conditioning the trade-off between sampling efficiency and precision. The fitting procedure employed in Rooy et al., 2021 was similar but unfolded through a three-step process : the first condition on keeping parameter sets was the numerically-computed bistability of the system, then the valid parameter space was further refined with a lenient ϵ according to the above equation, and after selecting the best candidate, the scaling factors A_x were introduced to further match the experimental data.

The main drawback of such techniques is the curse of dimensionality, as the parameter space cannot be fully explored. One is therefore not ensured to find a solution if there is one, which can impose hand-fitting from the best sampled parameter set as aforementioned, and even if a solution is found it is not guaranteed to be unique, since no information is acquired about the model's degeneracy.

Because a new parameter set was needed after the response function modifications and plasticity dynamics that we brought, and as a workaround to the above mentioned quandaries, we attempted fitting with a method developed by Greenberg, Nonnenmacher, and Macke, 2019, called Automatic Posterior Transformation. This technique belongs to the framework of conditional density estimation, which

A_e	A_p	A_s	Av
169	268	709	634

TABLE 2.1: Scaling factors

roughly consists in training an artificial neural network to estimate the distribution, conditioned to a certain data x , either of the synthetic likelihood $P(x|\theta)$ or directly of the posterior density $P(\theta|x)$. In a nutshell, the goal is to choose the appropriate function from a family of density functions q_ϕ parametrized by ϕ , such that $q_\phi \approx P(\theta|x)$. We thus train an artificial neural network F with weights σ such that $F(x, \sigma) = \phi$, by minimizing a loss function, in our case the opposite of the log-likelihood. The artificial neural network used was a masked autoregressive flow with default hyperparameters, which can be found in the code provided by Greenberg, Nonnenmacher, and Macke, 2019.

Besides the modifications in the model's structure earlier mentioned, we temporarily considered refractory periods (set to 8 ms for PYR neurons, 2ms for interneurons, according to Azouz et al., 1997 and Yang et al., 2018), as in the original Wilson Cowan's model, and set the factors A_x to their corresponding maximal population firing rate, i.e. the refractory period's inverse. This allows to more faithfully transform the "population activities" of the Wilson Cowan model, which stand for proportions of active cells in each population (thus with a maximum of 1) to actual firing rates, because as earlier stated, for increasing excitatory drive to a population x , and without divisive inhibition, its activity levels off to A_x . This way we reduced the degrees of freedom of the model to 10 weights, 4 external currents and the adaptation constant.

However, despite convergence of our neural network (Fig 2.1-C), the parameter set of maximal likelihood yielded a poor fit to the empirical data. Studying the distribution of euclidean distances of the synthetic data obtained through our 105 sampled parameter sets revealed that none of them got even close to it (minimal distance : 32). (Fig 2.1-D).

Fitting a stochastic oscillator on summary statistics requires long simulation windows to reduce the impact of noise in the estimation of the likelihood of a parameter set (800 seconds in our case). Furthermore, the many dimensions of our parameter space require many sets to be tested to get a chance to sample from the region of solutions. Taking into consideration the elevated computational cost of each simulation, partly due to their nonlinear dynamics which require small Euler timesteps (1ms), sums up to prohibitive processing expenditures for rigorous techniques of the SNPE framework. A major quandary is that we have no information about the existence of one or multiple solutions to our problem under the model's modifications that we brought. Nevertheless, approximate solutions do exist for the model resulting from giving up on the distinctions in refractory periods and corresponding values of scaling factors, as one was found through hand-fitting (Table 2.3). Yet, as we mentioned we have no information about the uniqueness of our solution and therefore about its validity.

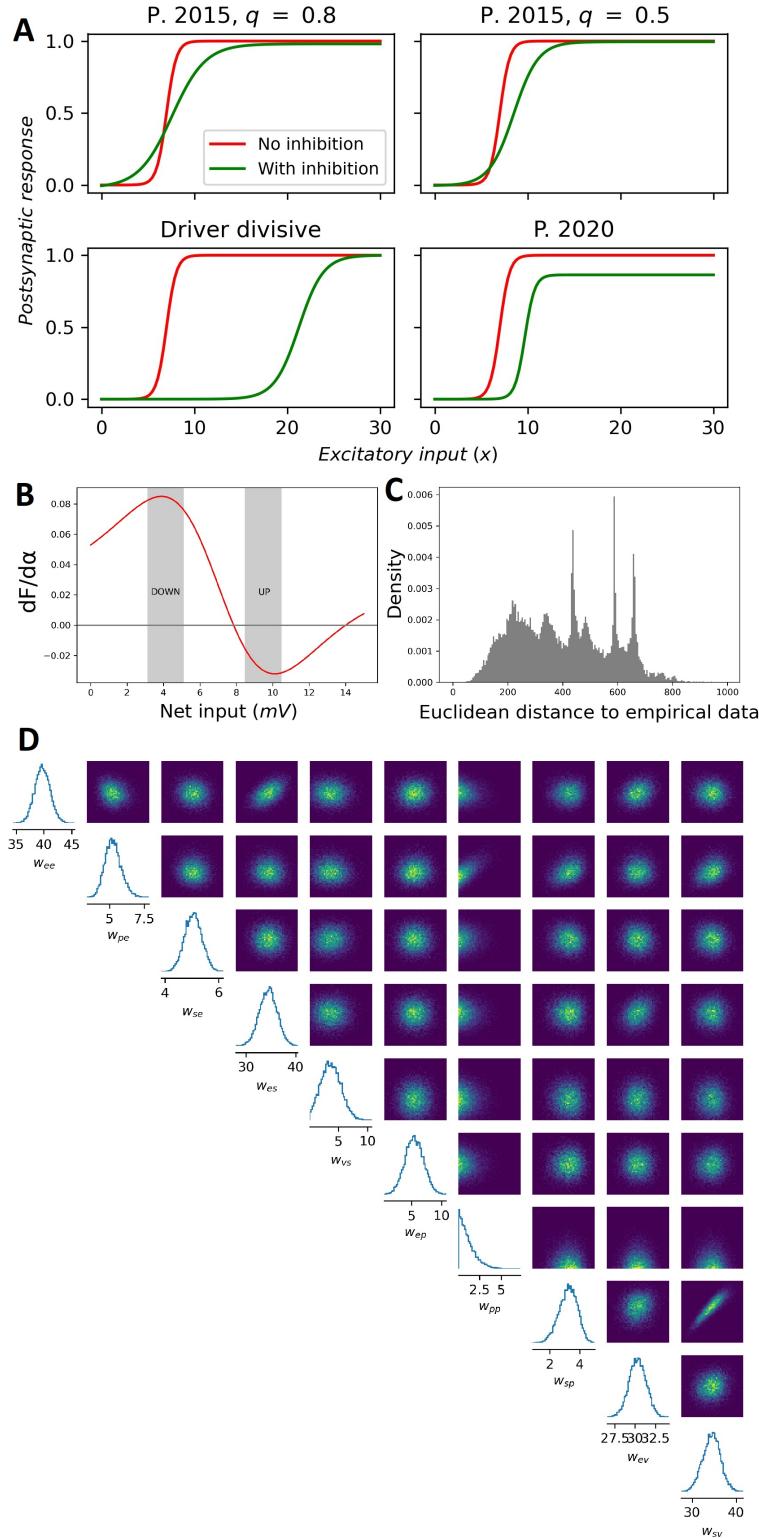


FIGURE 2.1: (A) - Comparative plots of different subpopulation response functions. x axis : net excitatory input. (B) Derivative of Papasavvas et al., 2015 subpopulation response function with respect to divisive inhibition, plotted as a function of PV's net output ($r_p \cdot \omega_{pe}$). Grey spans indicate typical values for DOWN and UP states. (C) Frequency histogram of Euclidean distances of simulated data's summary statistics to those of empirical data. (D) Example of posterior density plots for the weight parameters obtained through the SNPE-C method.

ω_{ee}/A_e	ω_{pe}/Ap	ω_{se}/A_s	ω_{ep}/A_e	ω_{pp}/Ap	ω_{vp}/A_v	ω_{es}/A_e	ω_{vs}/A_v
0.136	0.101	0.002	0.112	0.093	0.024	0.077	0.048
ω_{ev}/A_e	ω_{sv}/A_s	J_{adp}/A_e	I_{ext-e}	I_{ext-p}	I_{ext-s}	I_{ext-v}	q
0.041	0.001	0.056	3.9	4.5	3.6	2.9	0.8

TABLE 2.2: Selected parameter values for the initial model

ω_{ee}/A_e	ω_{pe}/Ap	ω_{se}/A_s	ω_{ep}/A_e	ω_{pp}/Ap	ω_{vp}/A_v	ω_{es}/A_e	ω_{vs}/A_v
0.136	0.075	0.045	0.17	0.093	0.016	0.053	0.04
ω_{ev}/A_e	ω_{sv}/A_s	J_{adp}/A_e	I_{ext-e}	I_{ext-p}	I_{ext-s}	I_{ext-v}	q
0.053	0.001	0.03	4.4	4.8	2.7	1.9	0.2

TABLE 2.3: Selected parameter values for the modified model

2.1.4 Two-populations model

The second part of the results is obtained with a model involving two symmetrical neural assemblies ('columns'), schematized in Figure 3.2-A. It basically consists of two dynamical systems which would be completely independent if it wasn't for their shared PV population (which therefore has almost twice as many input and output synapses as in the single-population model, with the exception of the single self-inhibitory synapse) and the introduction of two symmetrical connexions from one population's PYR to the other's SOM, of weights ω_{es} (equivalent to the corresponding connexion within each population), creating cross-columnar inhibition. To take into account these new connexions while preserving the modelled dynamics, external currents of SOM and PV populations were adapted the following way :

$$\begin{aligned} I_{ext-s} &\leftarrow I_{ext-s} - \omega_{es}r_e \\ I_{ext-p} &\leftarrow I_{ext-p} + \omega_{vp}r_v - \omega_{ep}r_e + \omega_{sp}r_s \end{aligned} \quad (2.16)$$

Where r_e and r_v correspond to the mean DOWN state firing rates detailed in Rooy et al., 2021, and r_s to the mean UP state ones, so that their external currents are better preserved when they are excited by the other population's active PYR neurons.

2.2 DMTS methods

In line with previous theoretical work (Dipoppa and Gutkin, 2013), we model the different steps of the DMTS as follows : first, the "cue" phase is represented by a thalamic excitatory transient delivered to PYR neurons, but also to PV and VIP populations (with half the amplitude of thalamus-to-PYR transients), as aforementioned. As compared to the previous model, the thalamic input is and explicitly defined step function instead of a Poisson-distributed Dirac-like input. We consider the detection to be successful when :

- The network remains in the UP state ($r_e > 20$ Hz) during the last 100ms of the "Load" period ([0ms, 300ms] after the transient stops), and
- The network was strictly in the DOWN state during the 100ms preceding cue onset.

A failure to either of these conditions results in a detection error (Figure 2.2-B). Then follows the retention period, which is considered successful (Figure 2.2-D) if:

- The detection was successful, *and*
- The network is still in the “UP” state during the last 100ms of the “Delay” period ([300ms, 2100ms] after the transient stops)

Otherwise resulting in a retention error (Figure 2.2-C). The main summary statistics we are interested in are therefore the probability of detecting the cue ($P(\text{detect})$) and the probability of successful retention ($P(\text{maintain})$). After having fitted most parameters of the model to experimental data, some parameters fundamental for task performance are yet to be determined. $P(\text{detect})$ heavily depends on the amplitude as well as on the duration of the transient, and as expected from the biological properties discussed in the introduction and included in the model, $P(\text{detect})$ is high for short transients of high amplitude, where feedforward inhibition doesn’t have time to fully unfold, as well as for long transients of low amplitude, in which PV input and output synapses depress and allow the triggering of the UP state (Figure 2.2-E). We chose an amplitude of 2.2 pA and a duration of 50ms, yielding a $P(\text{detect})$ close to 0.9. As pyramidal adaptation, over which $P(\text{maintain})$ heavily depends (Figure 2.2-F), is known to be slowed down by cholinergic tone (Cui and Stowbridge, 2019), we set the adaptation parameter J_{adp} to 5.07 so that $P(\text{maintain}) \approx 0.8$.

Nicotinic transients, in line with thalamic ones, were modelled as weighted step functions applying to $\beta 2$ -expressing populations (SOM and VIP neurons) under Bloem’s condition, and to VIP neurons under Kamigaki’s one, delivering 1-second long inputs starting at cue presentation. In order to model SOM’s non $\alpha 5$ -containing $\alpha 4\beta 2*$ nAChRs’ desensitization in Bloem’s condition, we simply applied equation 2.10’s depressing STP to the cholinergic nuclei-SOM synapses, with a first steady-state (in the absence of current) at $D = 1$ and a second steady-state at $D^{SS} = 0$. Current rectification (see section 1.3, second-to-last paragraph) was modelled by linearly weighting VIP’s nicotinic input by a factor N_r following :

$$N_r = 1 + \frac{(r_{v-UP}/2 - r_v)}{10} \quad (2.17)$$

Where r_{v-UP} approximates the typical UP-state firing rate of the VIP population, set to 60 Hz Rooy et al., 2021, so that N_r decreases below one halfway in the DOWN-to-UP state range of VIP activation.

2.3 Additional information

Shaded regions in every line plot represent two-tailed binomial 99% confidence intervals, and dashed vertical lines represent selected parameters.

Most of the simulations were performed on the SLURM-driven parallel computing cluster of the LNC² of the ENS, and classically involved 100 trials per data point.

All the code was written in Python3 and can be found online at : https://github.com/EliasElOtmani/wm_nachrs

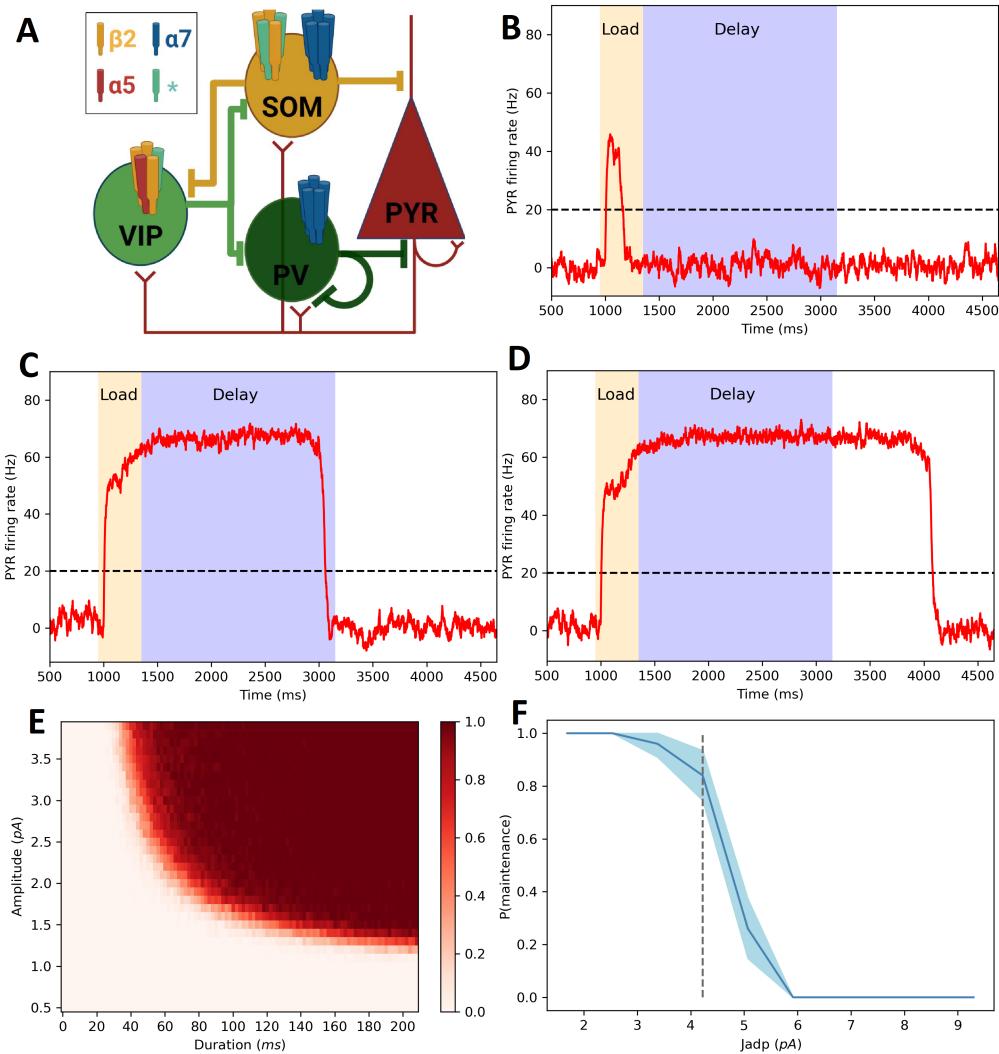


FIGURE 2.2: (A) Schematic representation of prefrontal supragranular microcircuitry. Forked presynaptic buttons are excitatory, the others are inhibitory. (B) Example of encoding error. (C) Example of retention error. (D) Example of DMTS success. (E) Heatmap of $P(\text{detect})$ depending on I_{trans} 's amplitude and duration. (F) $P(\text{maintainance})$ depending on the value of J_{adp} .

Chapter 3

Results

3.1 Cellular influences on DMTS performance - Minimal approaches

In this first part we compared the behavior of the initial model to the modified one (different divisive inhibition, introduction of STP and SOM-to-VIP synapses, different PV's membrane time constant), by evaluating the DMTS performance depending on each population's external current.

The initial model yields a trend towards enhancement of $P(\text{maintain})$ under nicotine, and a clear degradation first of $P(\text{detect})$ then $P(\text{maintain})$ as $I_{\text{ext-SOM}}$ increases, qualitatively reproducing the impairment in performance found in the literature. The effect is much stronger for $I_{\text{ext-PV}}$ and most importantly paradoxical, since detection and maintenance get monotonously enhanced as it increases. This is due to the divisive inhibition's initial implementation, as discussed in the Methods section. Accordingly, although VIP's SOM's inhibition is three times stronger than that of PVs, ω_{se} is 50 times lower than ω_{pe} so that we see the same paradoxical pattern, but inverted, for $I_{\text{ext-VIP}}$. Overall, variations in $I_{\text{ext-SOM}}$ seem to qualitatively reproduce empirical data, whereas manipulations of $I_{\text{ext-VIP}}$ and increases in $I_{\text{ext-PV}}$ don't. We can note that decreases in $I_{\text{ext-PV}}$ do reproduce the findings detailed in the introduction, yet this is obviously due to the technical reasons stated above rather than to the role of PVs in γ fluctuations.

The modified model yields a different picture, as every external current manipulation matches the experimental effects. The increase in ω_{se} not only displays a stronger effect of $I_{\text{ext-SOM}}$ on performance, but also suppresses the dissociation between $P(\text{detect})$ and $P(\text{maintain})$, an effect that was surprising since short term facilitation of SOM neurons was expected to confer them a stronger role in maintenance than in detection. Accordingly, the $\alpha 5$ SNP seems to foster detection errors, as expected from SCZ's phenotype, both through VIP's inhibition of SOM neurons and weakening of thalamocortical feedforward inhibition through PVs. We also observe an inverted-U shape of performance as a function of $I_{\text{ext-PV}}$, which very conveniently reproduces empirical findings, yet again this is obviously not due their role in γ oscillations but rather to a decrease in DOWN state's stability, as can be seen from the triggering of the UP state before cue onset in Figure 3.1-C (top) (recall that a detection is not considered successful if the network is already in the UP state at cue onset). Just as surprising as SOM neurons's effect in encoding, increases in PV's excitability impair faster maintenance than detection. Indeed, despite their short term depression, their divisive effect decreases the plateau of maximal PYR excitation, bringing their firing rates closer to the saddle point and therefore making the UP state more sensitive to noise. We also performed additional simulations on combined decreases in external currents, standing for $A\beta$ or general cholinergic

depletion effect, as well as their corresponding opposite external current changes, for illustrative purposes. Importantly, in these simulations the changes in I_{ext-PV} are 5 times weaker than those of $I_{ext-SOM}$ or $I_{ext-VIP}$, representing the weak nicotinic response of PV neurons. $A\beta$ simulations produce similar but stronger effects than variations in PV neurons' excitability, displaying an inverted U-shape. Since no dissociations appear between $P(\text{detect})$ and $P(\text{maintain})$ under $A\beta$, the results don't reproduce so far MCI's delay-dependent WM impairments (see section 1.4). Conversely, this pattern of impairments shows up for general cholinergic depletion, as we can observe intact encoding but worse retention, matching AD's clinical presentation. As can be seen in Figure 3.1-C (bottom), this is due to a reduction in the stability of both the DOWN and UP states, since in this example the cue easily triggers the UP state, which is also triggered without any cue at 3 seconds, but both UP states are only maintained for less than 1 second. The network is overall much more sensitive to any changes in external currents as opposed to the initial one in which PV neurons were dominant. Such a fragile equilibrium doesn't appear very biologically realistic, yet neither did the low to no effect on network function of $I_{ext-SOM}$ or $I_{ext-VIP}$ reduction from 2.5 pA (which represents respectively 70% and 86% of their default values).

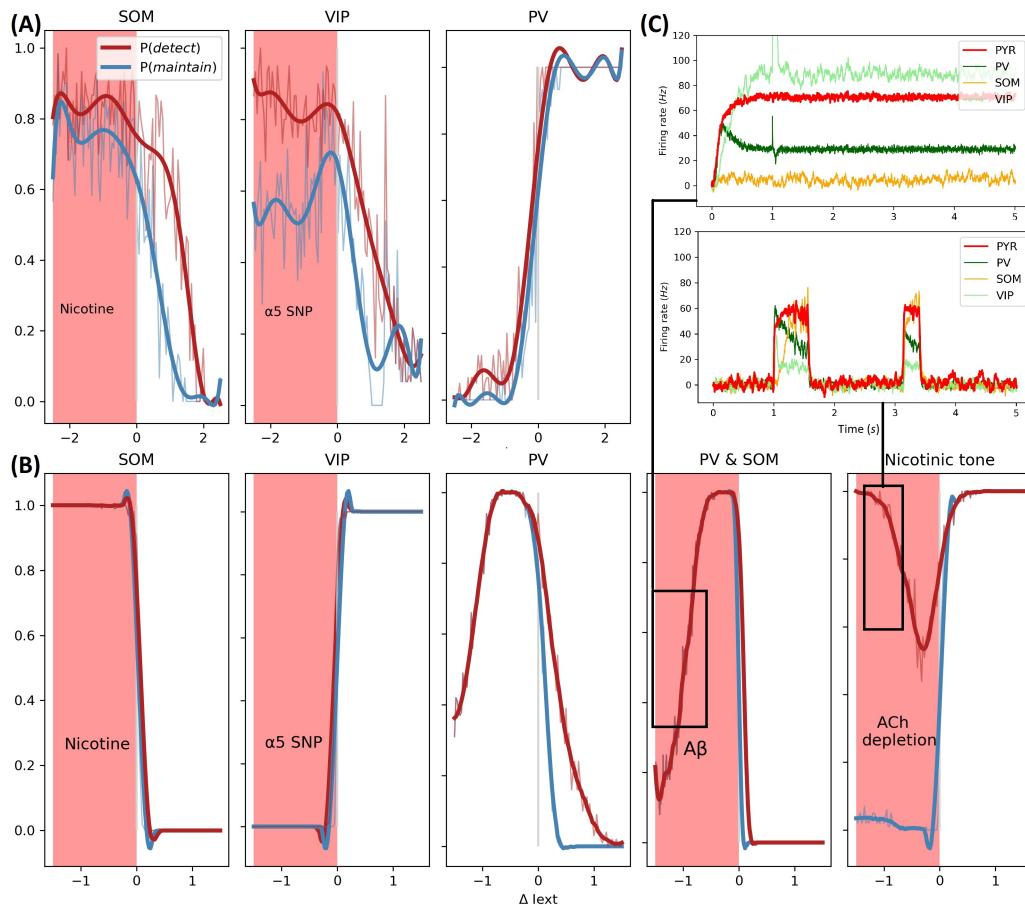


FIGURE 3.1: (A) Savitsky-Golay-filtered performance of the initial model as a function of SOM, VIP and PV external current. (B) Performance of the new model depending on SOM, VIP, PV, $I_{\alpha 7}$ and global nicotinic external current. (C) Example trials corresponding to $A\beta$ (top) and loss of nicotinic tone (bottom) situations

3.2 Distracted DMTS

We now use the two-populations model detailed in Chapter 2, and the same summary statistics to quantify performance. After successful encoding, a trial is considered a success if the trace resists against the distractor (Figure 3.2-B). A failed trial can either correspond to a simple disruption of the trace (3.2-C) or to, on top of it, encoding of the distractor (Figure 3.2-D). It seems that up to a certain point, the distractor's amplitude has a rather steady effect. It is therefore set to 2.2 pA, matching the cue's amplitude. The simulations yield similar overall results as compared to the single-population model (Figure 3.2-F). Yet, we do see that under nicotine, when $I_{ext-SOM}$ drops too low the model loses resistance against distractors despite intact encoding, reproducing empirical results. Accordingly, a symmetrical effect is found for VIP neurons. However, these effects are only observed for substantial differences in external currents, as a decrease in SOM neurons' excitability results in an initial increase in overall performance before distractors start impairing it. As a consequence, increasing $I_{ext-SOM}$ doesn't result in increased resistance against distractors here, as $P(detection)$ drops immediately, in disagreement with literature findings. Not surprisingly given the role of VIP neurons in detection and increased signal-to-noise ratio, the $\alpha 5$ SNP doesn't result in higher sensitivity against distractors (Figure 3.2-G), not reproducing the sensitivity to distraction documented in SCZ. Conversely, MCI results in equal or higher sensitivity to distraction as sole nicotine-mediated SOM inhibition, past a similar threshold of external current reduction, now in agreement with the clinical presentation of the disease (delay-dependent WM impairments and resistance against distractors).

3.3 Theories of phasic cholinergic release and attentional restoration by nicotine

In the previous section we mentioned that a trial's failure could correspond to an encoding of the distractor or not. As detailed in the introduction, it will be interesting to now study this phenomenon from a different viewpoint : the "distractor" takes place and gets encoded before cue onset, and encoding is successful if the cue gets detected despite the competing population being already in the UP state, corresponding to an attentional reorientation. We can observe that without any nicotinic transient involved ($I_{trans-ACh} = 0$, Figure 3.3-A), $P(detect) \approx 0.6$. Studying the effects of Bloem's and Kamigaki's hypothesis for different $I_{trans-ACh}$, with or without current rectification, points towards Bloem's condition (without current rectification) as the most robustly associated one with a very significant increase in $P(detect)$, over the widest range of $I_{trans-ACh}$. Current rectification is only detrimental to Bloem's condition, over all transient amplitudes with the exception of very low ones ($< 0.25\text{pA}$), but greatly increases the range of amplitudes over which Kamigaki's hypothesis is not detrimental to performance (which only entailed non biologically realistic amplitudes). Yet, despite current rectification, the apparent increase in performance under Kamigaki's condition remains non statistically significant. From now on, we will only consider Bloem's condition as not involving current rectification, and Kamigaki's one as including it.

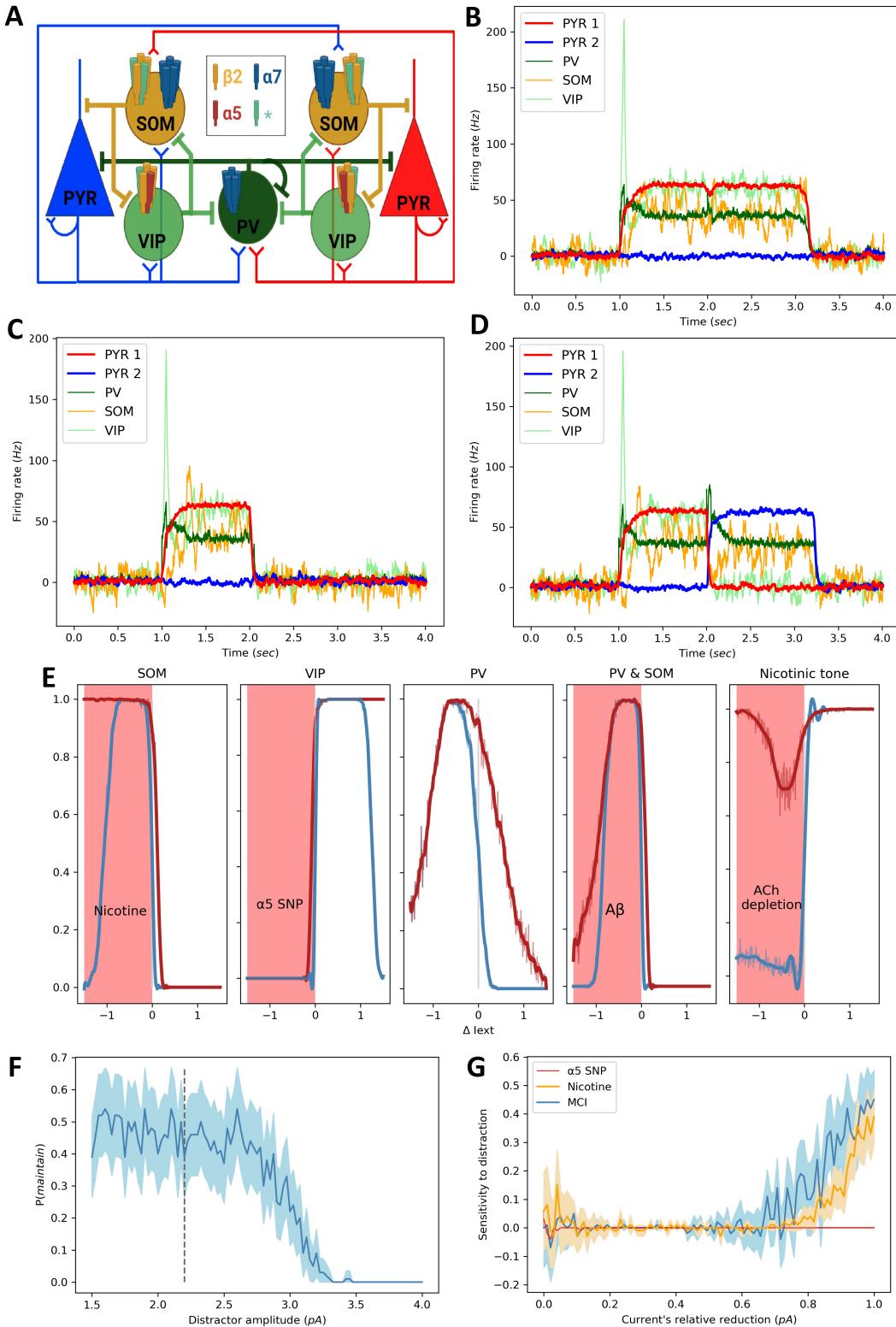


FIGURE 3.2: (A) Schematic microcircuitry of two competing populations in prefrontal supragranular layers. Red PYR population : cue-specific, blue : distractor-specific. (B) Example DMTS success through resistance against distractors. (C) Example of retention error without encoding of the distractor. (D) Example of retention error with encoding of the distractor. (E) dDMTS Savitsky-Golay-filtered performance as a function of neural population's external currents. (F) $P(maintain)$ as a function of the distractor's amplitude. (G) Relative effect of the distractor ($P(maintain)_{DMTS} / P(maintain)_{dDMTS}$) depending on different reductions in respective external currents.

Since the latter condition heavily relies on VIP neurons, it is the one most readily influenced by the $\alpha 5$ SNP, as can be seen in Figure 3.3-B. We can, however, note an initial protective effect of the reduction in VIP current, linked to an initial stronger decrease in the stability of the distractor's trace than in signal-to-noise ratio. We now choose a default transient amplitude of 0.75 pA, corresponding to the minimal value where both Bloem's and Kamigaki's conditions have reached their maximum performance. According to these results, we set the amplitude of the $\alpha 5$ SNP current reduction to 0.2 pA and 0.5 pA for Kamigaki's and Bloem's conditions, respectively, corresponding to detection probabilities lying in the]0, 0.1[interval. Studying the effect of increasing nicotine concentration (i.e., decreasing SOM excitability) under both conditions reveals that, interestingly, nicotine worsens detection in the healthy model but restores it under the $\alpha 5$ SNP (Figure 3.3-C), consistent with our table of empirical findings and with nicotine restoration of $\alpha 5$ SNP-induced hypofrontality in Koukouli et al., 2017. This falls from the opposite effects that SOMs & VIPs have on the excitatory / inhibitory balance.

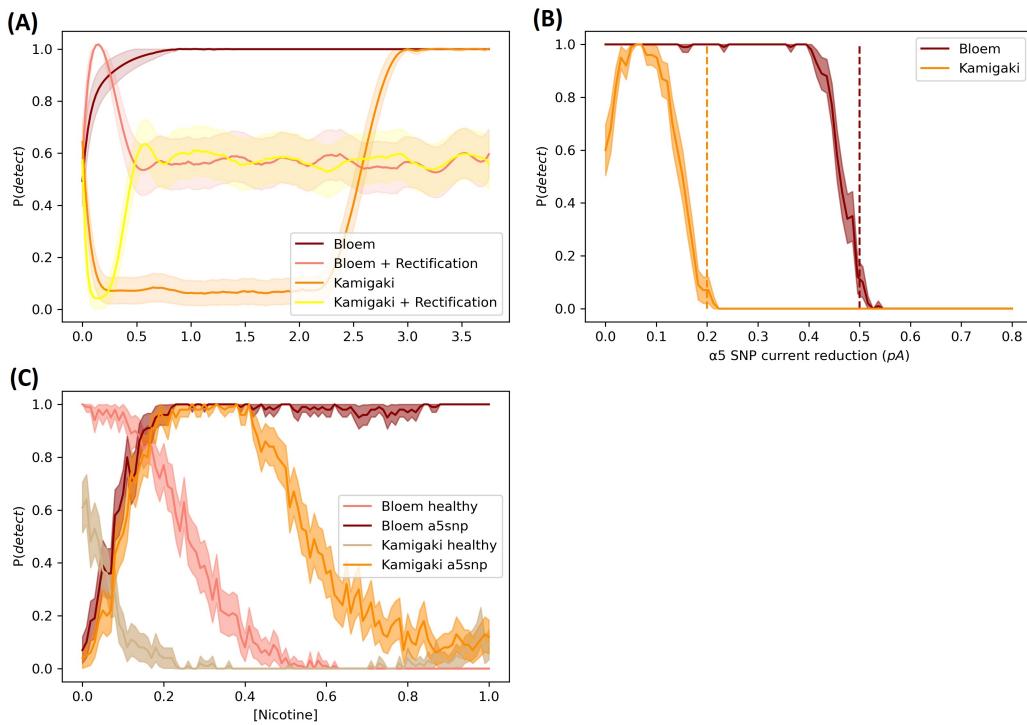


FIGURE 3.3: (A) $P(\text{encoding})$ as a function of nicotinic transient's amplitude, for Bloem against Kamigaki hypothesis, with and without nicotinic current rectification. (B) $\alpha 5$ SNP's effect on $P(\text{encoding})$ depending on Bloem against Kamigaki conditions. (C) $P(\text{encoding})$ depending on nicotine concentration (i.e. $I_{\text{ext-SOM}}$'s reduction) for healthy and $\alpha 5$ SNP models, for Bloem and Kamigaki conditions.

Chapter 4

Discussion

4.1 Cortical canonical model : general discussion & suggestions

The results shown in the present work are only preliminary and will need further experimental refinement. Most model parameters could be, at least in theory, assessed experimentally, yet we could only define on an empirical basis the weight ratios of VIP output synapses (Pi et al., 2013). Only thorough connectivity experiments in the mPFC, similar to studies carried out in the visual cortex (Pfeffer et al., 2013; Jiang et al., 2015) investigating both pairwise connexion probabilities and postsynaptic potential amplitudes, will allow to figure out the general connectivity matrix of mPFC's microcircuitry. The same kind of experiments could allow to explicitly fit STP parameters (both their time courses and plateau values), since the parameters that we assumed probably led to an underestimated STP (see Fanselow, Richardson, and Connors, 2008) considering the counterintuitive role that PVs and SOMs had on $P(\text{maintain})$ and $P(\text{detect})$ respectively (the latter even for very short thalamic transients).

Other assumed values which would deserve empirical fitting are the default parameters of the subpopulation response functions, namely the minimal displacement along the x axis and maximal slope, in order to take into account crucial electrophysiological features such as the low-threshold spiking property of SOM neurons. These cell type-specific considerations also apply for spike frequency adaptation, which should be fitted population-wise and, most importantly, should be also considered for VIP neurons (Tremblay, Lee, and Rudy, 2016). Also, the divisive effect of PVs on PYR should not only be fitted to empirical data, especially given its strong effects on the model's behavior, but also applied to the auto-inhibition of PVs since, at least in the PFC, their peri-somatal targeting property also applies when they target other PVs, as pointed out by Anastasiades and Carter, 2021. The latter review also states that PFC SOM neurons do receive thalamocortical input, contrary to what is said for the general neocortex in Tremblay, Lee, and Rudy, 2016. Finally, it would also be interesting to take into consideration NGFC, as not only do they represent 10% of supragranular interneurons, but they are also the most consistently nAChRs-depolarized ones (Bloem, Poorthuis, and Mansvelder, 2014). In the long run, applying as many of these considerations as possible might allow to virtually constrain the model down to the four-dimensional external currents' parameter space.

These considerations are important because quantitative differences in the connectivity matrix or electrophysiological properties can lead to qualitative functional changes depending on the region and situation of interest, as for example a subset of PV cells can under certain conditions be excitatory, SOM neurons are disinhibitory (through PVs) rather than inhibitory of PYR in subgranular layers (Tremblay, Lee,

and Rudy, 2016) while the opposite is true for some VIP neurons in the premotor cortex (i.e. direct inhibition of PYR, Garcia-Juncos-Clemente et al., 2017), not to mention the ambiguous effects of NGFC's volume inhibition.

With only a handful of parameters to infer, the SNPE approach that we tried in this work (and its probable future refinements, given the speed at which the simulation-based inference field grows) appears as an ideal option to go for. This will however require adequate empirical data, namely population's mean firing rates in contexts of working memory or sustained attention tasks, as are being prepared in our collaborative team at Institut Pasteur. Indeed, not only the resting-state empirical data that we used probably corresponds to very different levels of neuromodulation and network state, but even the analogy between USFs and delay-related working memory activity has its limits, as for example the former involves large portions of the cortex where nearly 80% of cells show synchronized activity (Koukouli, Rooy, and Maskos, 2016) whereas WM mechanisms encompass sparser assemblies of 30% of pyramidal cells (Constantinidis et al., 2018), this fact being particularly important at the time of considering the connection patterns between two competing populations.

Beyond these possible modifications, we should also mention the inherent limitations of rate models in this context. The major quandary concerns the fast and subtle dynamics of PVs, involving coincidence detection and strong STP at the level of single spikes, playing a key role in promoting WM-related γ oscillations. Even though PVs, as cells unresponsive to nicotinic stimulation, are not the most interesting population in the scope of this work, their muscarinic- (Kruglikov and Rudy, 2008) and indirect nicotinic NGFC-mediated presynaptic inhibitions (Tremblay, Lee, and Rudy, 2016) are known to play a role in weakening feed-forward inhibition of PYR, enhancing thalamocortical processing. Interestingly, while both cholinergic modulation and attention are shown to foster cortical desynchronization (Chen, Sugihara, and Sur, 2015; Harris and Thiele, 2011), consistent with inhibition of PVs, Sarter's hypothesis for the role of cholinergic transients (Sarter and Lustig, 2019) conversely involves promoting γ oscillations, also with empirical support in the prefrontal cortex (Howe et al., 2017). If at some point muscarinic inhibition is to be taken into account in order to investigate these discrepancies, it will be necessary to set up a spiking model to better capture PVs fast kinematics as well as network oscillations. Furthermore, it is still a matter of debate whether their shunting effect really translates into divisive inhibition at the population level (Papasavvas et al., 2020) or not (Holt and Koch, 1997). Yet, the rate model remains ideal when restricting the analysis to nicotinic modulation in the mPFC (where SOM and VIP neurons are four to five times as many as PVs, see Kim et al., 2017), and constitutes a robust way of bridging the gap between what is known about nAChRs at the molecular level and their cognitive role.

4.2 Nicotinic modulation of cognition in the mPFC

A picture is slowly emerging for the role of nicotinic neuromodulation in supragranular layers of the PFC. Contrary to the old view of cholinergic modulation solely as a slow and diffuse process, acting through volume transmission to inform the cortex about the general emotional state of the animal, it appears today as functioning through two different components subserving two distinct functions (Sarter and Lustig, 2019). Tonic acetylcholine linked to cognitive effort fosters resistance against distractors and stabilization of the content of working memory, presumably through

SOM-mediated disynaptic inhibition. By contrast, time-locked phasic acetylcholine acts on top of tonic modulation and over shorter timescales to promote attentional reorientations. These transients are thought to result from top-down mechanisms, as the relevant triggering cues are determined by the ongoing activity in the PFC, which represents the task demands. For example, during a visual search task where an animal has to press a lever once it finds a certain cue, it will maintain the first rule (looking for the cue) in working memory while tonic ACh stabilizes it against distraction ; this higher-order representation will act on posterior cortices to determine which features should be attended to, but will also promote the association of the expected cue to the elicitation of a cholinergic transient, through unknown mechanisms. The latter will be triggered immediately after the cue is found, resetting the current rule held in working memory and promoting its replacement by the second rule, i.e. lever press and reward expectation. However, since salient cues are known to activate brain stem's cholinergic nuclei (Lin and Nicolelis, 2008), transients could be in all likelihood also triggered by bottom-up mechanisms, where for example the presentation of unexpected but potentially dangerous unconditioned cues (such as a predator's silhouette) involves giving up on the current task and dedicating cognitive resources to defense behaviors.

It is not clear which circuit mechanisms are responsible for the effect of the transient. However, our preliminary results point towards a higher efficiency of Bloem's hypothesis for most transient's amplitudes, which is also backed up by more empirical data and by the abundance of SOM neurons in the PFC. Assessing the efficacy of these transients in rodents expressing the $\alpha 5$ SNP will provide strong empirical support in favor of one or the other hypothesis. Beyond the circuit mechanisms, it remains remarkable that the very same modulator can either inhibit the processing of distractors, stabilizing working memory, and conversely favor the detection of cues to the detriment of the current mental representation, depending on its concentration and timing.

It is worth mentioning that our work only considers alterations in external currents, neglecting the other roles that nAChRs are known to endorse. For example, the $\beta 2$ subunit plays a role in neural survival as well as in STP through pre-synaptic expression, whereas the $\alpha 5$ one is involved in neurodevelopment, and its knock-out leads to shorter pyramidal apical dendrites (Bloem, Poorthuis, and Mansvelder, 2014), which interestingly corresponds to histological findings of post-mortem studies of patients with schizophrenia, independently of specific $\alpha 5$ SNP screening (Koluri et al., 2005).

Since we only considered rodent neurophysiology, we largely neglected homomeric $\alpha 7$ nAChRs in this work. However, they are known to play a fundamental role in primates, which express them in the postsynaptic densities of PYR neurons in deep layer III of the dorsolateral PFC, where WM circuits were first identified. Importantly, they seem to act as a substitute for the role of the AMPA glutamate receptors, nearly absent in the PFC (Yang et al., 2013). The activation of $\alpha 7$ receptors thus allows, past a certain threshold, to relieve NMDA receptors from their magnesium block, which in turn unchains recurrent excitation mechanisms necessary for WM (Goldman-Rakic, 1995). One could therefore speculate that the lower affinity of $\alpha 7$ nAChRs to ACh as compared to $\alpha 4\beta 2*$ ones could grant them a specific role of activating at high ACh concentrations, i.e. during cholinergic transients, fostering NMDA-mediated supralinear effects allowing the encoding of new information into WM. It is noteworthy that mutations in the $\alpha 7$ receptor are highly prevalent in SCZ (Psychiatric Genomics Consortium, 2014).

4.3 $\alpha 5$ SNP and other nicotinic impairments

Our minimal approach to the DMTS, without distractors, matched all the empirical findings we set up to reproduce about the influence of different INs types on WM. Up to this point, global nicotinic neuromodulation seemed to mostly stabilize both the DOWN and UP states, since loss of nicotinic tone translated into higher detection rates but lower retention, in agreement with the delay-dependent WM impairments of declared AD. This same WM phenotype during MCI was not reproduced by our model, since we essentially observed an impairment in cue detection. From this viewpoint, our results don't support the hypothesis of the $\alpha 7 - A\beta$ pathophysiology. Conversely, the fact that the $\alpha 5$ SNP resulted mostly in detection errors was consistent with the clinical presentation of SCZ and with the suggestion in Rooy et al., 2021 of this alteration as undermining the propensity of the network to reach the UP states. Including the presence of distractors to the analysis reproduces the expected sensitivity to distraction as SOM neurons' excitability decreases which, from the functional point of view, can be seen as a generalization of above discussed stabilizing effects that nicotinic neuromodulation has on the UP states. This effect is however not spectacular in our results, and most importantly we failed to reproduce the improvements in resistance against distractors mediated by SOM neurons' increase in excitability. Regarding SCZ, the clinical phenotype seems to involve a lower resistance against distraction, which our drastic reduction in $P(\text{detect})$ didn't allow to reproduce. In the lower half of the $A\beta$ condition, sensitivity to distraction did decrease faster than the detection errors, bringing these results closer to MCI's phenotype of delay- and distraction-dependent WM impairments.

The opposite effect of current rectification under Bloem's and Kamigaki's condition is due to the fact that SOM neurons of both populations are active at any time, making the effect of current rectification lighter (and even detrimental, since the silent population has the most active SOM neurons) in the former condition, whereas in Kamigaki's condition VIP cells of the relevant population are not active, thus they are the most enhanced ones as opposed to those of the irrelevant population. Despite the $\alpha 5$ SNP having a much stronger effect in attentional reorientation under Kamigaki's condition than under Bloem's one, our results support the latter theory as being more robust and effective. This would suggest that $\alpha 5$ SNP-mediated impairments are not linked to problems in attentional orientation, but rather to its general effect in VIP-mediated increase in signal-to-noise, which showed up in our previous conditions. Although quite speculative, this seems to be in agreement with the phenotype of detection impairments despite intact attentional control mentioned in the introduction (section 1.4). Furthermore, the performance enhancement that we observed under nicotine supports the self-medication hypothesis of heavy smoking in SCZ, suggesting that beyond restoration of hypofrontality (Koukouli et al., 2017), WM is restored as well. We can note that the self-medication hypothesis is also consistent with smoking addiction without SCZ, to which the $\alpha 5$ SNP also predisposes, since, as we discussed, the latter also correlated with WM impairments in the absence of any declared disease.

We previously pointed out discrepant findings in the literature (see 1.2) about the effects of nicotine on cognition of non-smokers (Kleykamp et al., 2005) : it appears to affect human WM but not attention in Park et al., 2000, whereas Howe et al., 2010 point to attentional impairments in rodents. Conversely, similar methods in Mirza and Stolerman, 1998 yielded attentional enhancements under some conditions, Sacco et al., 2005 show a positive effect in patients with SCZ, and Rezvani

and Levin, 2001 and Barr et al., 2008 indicate an attentional and mnemonic enhancement even in healthy individuals. In our model, increasing nicotine concentration strictly enhanced performance in the minimal approach, increased then decreased performance under distractors, and strictly decreased performance in the attention-reorientation condition for the healthy model, which suggest that along with the obvious relieving effect on withdrawal-induced deficits in smokers (Lawrence, Ross, and Stein, 2002), the discrepant findings about the consequences of nicotine administration might be due both to different genetic profiles (recall that a third of European population expresses the $\alpha 5$ SNP), the dose of administered nicotine, and also to the structure of the task, depending on whether it involves distractors or attentional shifts.

4.4 Predictions

As stated in section 4.1, our model's parameters still lack robustness and empirical back up. Yet, after having reproduced part of the experimental results and notably those of cellular and nicotinic manipulations in mice, we can begin to formulate the following predictions, left to further refinement, regarding what has not been empirically tested to this day :

- Mice electrophysiological or calcium imaging PrLC recordings with identified interneuronal types should show dominant and most importantly short activation of SOM neurons during cue-evoked cholinergic transients.
- During attentional tasks, optogenetic transient activation of SOM neurons at cue onset should mimic the attention-reorientation effects of phasic cholinergic release.
- In mice, PrLC nicotine infusion should decrease resistance against distractors at high concentrations.
- In $\alpha 5$ -KO or $\alpha 5$ SNP-expressing mouse models, PrLC nicotine infusion should improve attentional performance and thus WM, with a larger effect than in wild-type mice.

The above-mentioned predictions are the most important ones, since they are related with specific PrLC of mPFC manipulations. Indeed, the nicotinic system bears high importance many other parts of the brain such as the hippocampus, which is also incriminated in SCZ. Tearing apart PFC effects of general nicotinic impairments from other regional effects is therefore not straightforward. The following predictions should thus be taken as simple suggestions of the model, if PFC deficits indeed are the dominant effects of the $\alpha 5$ SNP :

- Subjects expressing the $\alpha 5$ SNP should show delay-independent WM deficits such as in SCZ.
- Subjects expressing the $\alpha 5$ SNP should not show comparatively higher deficits in cue detection under attentional reorientation than under classical cue-detection tasks.

Chapter 5

Conclusion

Our modelling framework allowed us to qualitatively reproduce almost all the observed cognitive consequences of electrophysiological, genetic, optogenetic and pharmacological manipulations of INs' excitability found in the literature. Considering these modifications in the context of mental illnesses matched the clinical phenotypes of detection errors, but not this of sensitivity to distraction, in SCZ, and of sensitivity against distractors, but not this of retention errors, in MCI. Importantly, the modelled effect of nicotine enhanced WM only in the $\alpha 5$ SNP condition, providing a mechanistic basis for the self-medication hypothesis of heavy smoking in SCZ and tobacco addiction. From our literature review and results stems evidence for a dual role of nicotinic neuromodulation. In the context of attentional and WM tasks, tonic modulation seems to stabilize the content of WM (including goal and rule representations and top-down attentional control), especially when the latter is threatened by distraction. Conversely, higher concentrations of ACh, during cholinergic transients, allows the clearance of the current representations and the encoding of new ones. Our results suggest that this effect might be due to an initial fast resetting of the network through stronger activation of SOM than VIP neurons, quickly followed by a facilitation of the encoding through VIP neurons, once SOM neurons' nAChRs have desensitized. It should be kept in mind that our results mostly involve binary statistics (i.e. increases or decreases in encoding and retention performance, since the model is so sensitive to perturbations that the "no effect" result virtually doesn't exist), therefore the reproduction of the empirical data shouldn't be seen as a proxy for the validity of the model. Many modifications and experimental back up will be needed in order to confer robustness to the results. Nevertheless, our data so far provides an interesting proof of concept for a unified account of nicotinic neuromodulation of prefrontal network function.

Bibliography

- Abbas, Atheir I. et al. (2018). "Somatostatin Interneurons Facilitate Hippocampal-Prefrontal Synchrony and Prefrontal Spatial Encoding". In: *Neuron* 100.4, 926–939.e3. ISSN: 0896-6273. DOI: <https://doi.org/10.1016/j.neuron.2018.09.029>. URL: <https://www.sciencedirect.com/science/article/pii/S0896627318308316>.
- Anastasiades, Paul G. and Adam G. Carter (2021). "Circuit organization of the rodent medial prefrontal cortex". In: *Trends in Neurosciences* 44.7, pp. 550–563. ISSN: 0166-2236. DOI: <https://doi.org/10.1016/j.tins.2021.03.006>. URL: <https://www.sciencedirect.com/science/article/pii/S0166223621000722>.
- Arnsten, Amy F.T. et al. (2010). "Dynamic Network Connectivity: A new form of neuroplasticity". In: *Trends in Cognitive Sciences* 14.8, pp. 365–375. ISSN: 1364-6613. DOI: <https://doi.org/10.1016/j.tics.2010.05.003>. URL: <https://www.sciencedirect.com/science/article/pii/S1364661310001117>.
- Arroyo, Sergio, Corbett Bennett, and Shaul Hestrin (2014). "Nicotinic modulation of cortical circuits". In: *Frontiers in Neural Circuits* 8, p. 30. ISSN: 1662-5110. DOI: [10.3389/fncir.2014.00030](https://doi.org/10.3389/fncir.2014.00030). URL: <https://www.frontiersin.org/article/10.3389/fncir.2014.00030>.
- Auerbach, Anthony and Gustav Akk (Aug. 1998). "Desensitization of Mouse Nicotinic Acetylcholine Receptor Channels : A Two-Gate Mechanism". In: *Journal of General Physiology* 112.2, pp. 181–197. ISSN: 0022-1295. DOI: [10.1085/jgp.112.2.181](https://doi.org/10.1085/jgp.112.2.181). eprint: <https://rupress.org/jgp/article-pdf/112/2/181/1191211/7697.pdf>. URL: <https://doi.org/10.1085/jgp.112.2.181>.
- Azouz, R et al. (Sept. 1997). "Physiological properties of inhibitory interneurons in cat striate cortex." In: *Cerebral Cortex* 7.6, pp. 534–545. ISSN: 1047-3211. DOI: [10.1093/cercor/7.6.534](https://doi.org/10.1093/cercor/7.6.534). eprint: <https://academic.oup.com/cercor/article-pdf/7/6/534/9752596/070534.pdf>. URL: <https://doi.org/10.1093/cercor/7.6.534>.
- Bailey, Craig D. C. et al. (2010). "The Nicotinic Acetylcholine Receptor 5 Subunit Plays a Key Role in Attention Circuitry and Accuracy". In: *Journal of Neuroscience* 30.27, pp. 9241–9252. ISSN: 0270-6474. DOI: [10.1523/JNEUROSCI.2258-10.2010](https://doi.org/10.1523/JNEUROSCI.2258-10.2010). eprint: <https://www.jneurosci.org/content/30/27/9241.full.pdf>. URL: <https://www.jneurosci.org/content/30/27/9241>.
- Barr, Ruth S. et al. (2008). "The Effects of Transdermal Nicotine on Cognition in Non-smokers with Schizophrenia and Nonpsychiatric Controls". In: *Neuropsychopharmacology* 33.3, pp. 480–490. ISSN: 1740-634X. DOI: [10.1038/sj.npp.1301423](https://doi.org/10.1038/sj.npp.1301423). URL: <https://doi.org/10.1038/sj.npp.1301423>.
- Belleville, Sylvie et al. (2008). "Chapter 23 Characterizing the memory changes in persons with mild cognitive impairment". In: *Essence of Memory*. Ed. by Wayne S. Sossin et al. Vol. 169. Progress in Brain Research. Elsevier, pp. 365–375. DOI: [https://doi.org/10.1016/S0079-6123\(07\)00023-4](https://doi.org/10.1016/S0079-6123(07)00023-4). URL: <https://www.sciencedirect.com/science/article/pii/S0079612307000234>.
- Berger, Christoph et al. (2015). "Effects of Task-Irrelevant Emotional Stimuli on Working Memory Processes in Mild Cognitive Impairment". In: *Journal of Alzheimer's*

- Disease* 44. 2, pp. 439–453. ISSN: 1875-8908. DOI: [10.3233/JAD-141848](https://doi.org/10.3233/JAD-141848). URL: <https://doi.org/10.3233/JAD-141848>.
- Bloem, Bernard, Rogier Poorthuis, and Huibert Mansvelder (2014). “Cholinergic modulation of the medial prefrontal cortex: the role of nicotinic receptors in attention and regulation of neuronal activity”. In: *Frontiers in Neural Circuits* 8, p. 17. ISSN: 1662-5110. DOI: [10.3389/fncir.2014.00017](https://doi.org/10.3389/fncir.2014.00017). URL: <https://www.frontiersin.org/article/10.3389/fncir.2014.00017>.
- Castner, Stacy A. et al. (2011). “Immediate and Sustained Improvements in Working Memory After Selective Stimulation of 7 Nicotinic Acetylcholine Receptors”. In: *Biological Psychiatry* 69.1. N-Methyl-D-Aspartate Receptor Function and Cortical Connectivity in Schizophrenia, pp. 12–18. ISSN: 0006-3223. DOI: <https://doi.org/10.1016/j.biopsych.2010.08.006>. URL: <https://www.sciencedirect.com/science/article/pii/S0006322310008231>.
- Chen, Naiyan, Hiroki Sugihara, and Mriganka Sur (2015). “An acetylcholine-activated microcircuit drives temporal dynamics of cortical activity”. In: *Nature Neuroscience* 18.6, pp. 892–902. ISSN: 1546-1726. DOI: [10.1038/nn.4002](https://doi.org/10.1038/nn.4002). URL: <https://doi.org/10.1038/nn.4002>.
- Constantinidis, Christos et al. (2018). “Persistent Spiking Activity Underlies Working Memory”. In: *Journal of Neuroscience* 38.32, pp. 7020–7028. ISSN: 0270-6474. DOI: [10.1523/JNEUROSCI.2486-17.2018](https://doi.org/10.1523/JNEUROSCI.2486-17.2018). eprint: <https://www.jneurosci.org/content/38/32/7020.full.pdf>. URL: <https://www.jneurosci.org/content/38/32/7020>.
- Cossart, Rosa, Dmitriy Aronov, and Rafael Yuste (2003). “Attractor dynamics of network UP states in the neocortex”. In: *Nature* 423.6937, pp. 283–288. ISSN: 1476-4687. DOI: [10.1038/nature01614](https://doi.org/10.1038/nature01614). URL: <https://doi.org/10.1038/nature01614>.
- Cui, Edward D and Ben W Strowbridge (2019). “Selective attenuation of Ether-a-go-go related K⁺ currents by endogenous acetylcholine reduces spike-frequency adaptation and network correlation”. In: *eLife* 8. Ed. by Julie A Kauer, Richard Aldrich, and Lorna Role, e44954. ISSN: 2050-084X. DOI: [10.7554/eLife.44954](https://doi.org/10.7554/eLife.44954). URL: <https://doi.org/10.7554/eLife.44954>.
- Dani, John A. and Daniel Bertrand (2007). “Nicotinic Acetylcholine Receptors and Nicotinic Cholinergic Mechanisms of the Central Nervous System”. In: *Annual Review of Pharmacology and Toxicology* 47.1. PMID: 17009926, pp. 699–729. DOI: [10.1146/annurev.pharmtox.47.120505.105214](https://doi.org/10.1146/annurev.pharmtox.47.120505.105214). eprint: <https://doi.org/10.1146/annurev.pharmtox.47.120505.105214>. URL: <https://doi.org/10.1146/annurev.pharmtox.47.120505.105214>.
- Di Giorgio, Annabella et al. (May 2014). “DRD2/CHRNA5 Interaction on Prefrontal Biology and Physiology during Working Memory”. In: *PLOS ONE* 9.5, pp. 1–12. DOI: [10.1371/journal.pone.0095997](https://doi.org/10.1371/journal.pone.0095997). URL: <https://doi.org/10.1371/journal.pone.0095997>.
- Dienel, Samuel J. and David A. Lewis (2019). “Alterations in cortical interneurons and cognitive function in schizophrenia”. In: *Neurobiology of Disease* 131. What can clinical findings tell us about the neurobiology of schizophrenia? Revisited, p. 104208. ISSN: 0969-9961. DOI: <https://doi.org/10.1016/j.nbd.2018.06.020>. URL: <https://www.sciencedirect.com/science/article/pii/S0969996118301992>.
- Dipoppa, Mario and Boris S. Gutkin (2013). “Flexible frequency control of cortical oscillations enables computations required for working memory”. In: *Proceedings of the National Academy of Sciences* 110.31, pp. 12828–12833. ISSN: 0027-8424. DOI: [10.1073/pnas.1303270110](https://doi.org/10.1073/pnas.1303270110). eprint: <https://doi.org/10.1073/pnas.1303270110>. URL: <https://doi.org/10.1073/pnas.1303270110>.

- Fanselow, Erika E., Kristen A. Richardson, and Barry W. Connors (2008). "Selective, State-Dependent Activation of Somatostatin-Expressing Inhibitory Interneurons in Mouse Neocortex". In: *Journal of Neurophysiology* 100.5. PMID: 18799598, pp. 2640–2652. DOI: [10.1152/jn.90691.2008](https://doi.org/10.1152/jn.90691.2008). eprint: <https://doi.org/10.1152/jn.90691.2008>. URL: <https://doi.org/10.1152/jn.90691.2008>.
- Ferguson, Brielle R. and Wen-Jun Gao (2018). "PV Interneurons: Critical Regulators of E/I Balance for Prefrontal Cortex-Dependent Behavior and Psychiatric Disorders". In: *Frontiers in Neural Circuits* 12, p. 37. ISSN: 1662-5110. DOI: [10.3389/fncir.2018.00037](https://doi.org/10.3389/fncir.2018.00037). URL: <https://www.frontiersin.org/article/10.3389/fncir.2018.00037>.
- Fino, Elodie, Adam M. Packer, and Rafael Yuste (2013). "The Logic of Inhibitory Connectivity in the Neocortex". In: *The Neuroscientist* 19.3. PMID: 22922685, pp. 228–237. DOI: [10.1177/1073858412456743](https://doi.org/10.1177/1073858412456743). eprint: <https://doi.org/10.1177/1073858412456743>. URL: <https://doi.org/10.1177/1073858412456743>.
- Forbes, N. F. et al. (2009). "Working memory in schizophrenia: a meta-analysis". In: *Psychological Medicine* 39.6, 889–905. DOI: [10.1017/S0033291708004558](https://doi.org/10.1017/S0033291708004558).
- Fukuda, Takaichi et al. (2006). "Gap Junctions among Dendrites of Cortical GABAergic Neurons Establish a Dense and Widespread Intercolumnar Network". In: *Journal of Neuroscience* 26.13, pp. 3434–3443. ISSN: 0270-6474. DOI: [10.1523/JNEUROSCI.4076-05](https://doi.org/10.1523/JNEUROSCI.4076-05). 2006. eprint: <https://www.jneurosci.org/content/26/13/3434.full.pdf>. URL: <https://www.jneurosci.org/content/26/13/3434>.
- Gagnon, L. G. and S. Belleville (2011). "Working memory in mild cognitive impairment and Alzheimer's disease: contribution of forgetting and predictive value of complex span tasks". In: *Neuropsychology* 25.2, pp. 226–236. DOI: [10.1037/a0020919](https://doi.org/10.1037/a0020919). URL: <https://pubmed.ncbi.nlm.nih.gov/21090897/>.
- Garcia-Junco-Clemente, Pablo et al. (2017). "An inhibitory pull-push circuit in frontal cortex". In: *Nature Neuroscience* 20.3, pp. 389–392. ISSN: 1546-1726. DOI: [10.1038/nn.4483](https://doi.org/10.1038/nn.4483). URL: <https://doi.org/10.1038/nn.4483>.
- Gold, James M. et al. (2006). "Intact attentional control of working memory encoding in schizophrenia". In: *Journal of Abnormal Psychology* 115.4, pp. 658–673. DOI: [10.1037/0021-843X.115.4.658](https://doi.org/10.1037/0021-843X.115.4.658). URL: <https://doi.org/10.1037/0021-843X.115.4.658>.
- Gold, James M. et al. (June 2010). "Reduced Capacity but Spared Precision and Maintenance of Working Memory Representations in Schizophrenia". In: *Archives of General Psychiatry* 67.6, pp. 570–577. ISSN: 0003-990X. DOI: [10.1001/archgenpsychiatry.2010.65](https://doi.org/10.1001/archgenpsychiatry.2010.65). eprint: <https://jamanetwork.com/journals/jamapsychiatry/articlepdf/210810/yoa90106\570\577.pdf>. URL: <https://doi.org/10.1001/archgenpsychiatry.2010.65>.
- Goldman-Rakic, P.S (1995). "Cellular basis of working memory". In: *Neuron* 14.3, pp. 477–485. ISSN: 0896-6273. DOI: [https://doi.org/10.1016/0896-6273\(95\)90304-6](https://doi.org/10.1016/0896-6273(95)90304-6). URL: <https://www.sciencedirect.com/science/article/pii/0896627395903046>.
- Gotti, C. and F. Clementi (2004). "Neuronal nicotinic receptors: from structure to pathology". In: *Progress in Neurobiology* 74.6, pp. 363–396. ISSN: 0301-0082. DOI: <https://doi.org/10.1016/j.pneurobio.2004.09.006>. URL: <https://www.sciencedirect.com/science/article/pii/S0301008204001777>.
- Greenberg, David, Marcel Nonnenmacher, and Jakob Macke (2019). "Automatic Posterior Transformation for Likelihood-Free Inference". In: *Proceedings of the 36th International Conference on Machine Learning*. Ed. by Kamalika Chaudhuri and Ruslan Salakhutdinov. Vol. 97. Proceedings of Machine Learning Research. PMLR, pp. 2404–2414. URL: <http://proceedings.mlr.press/v97/greenberg19a.html>.

- Guan, Zhi-Zhong et al. (1999). "Decreased protein level of nicotinic receptor $\alpha 7$ subunit in the frontal cortex from schizophrenic brain". In: *NeuroReport* 10.8. ISSN: 0959-4965. URL: https://journals.lww.com/neuroreport/Fulltext/1999/06030/Decreased_protein_level_of_nicotinic_receptor_7.28.aspx.
- Guillem, Karine et al. (2011). "Nicotinic Acetylcholine Receptor 2 Subunits in the Medial Prefrontal Cortex Control Attention". In: *Science* 333.6044, pp. 888–891. ISSN: 0036-8075. DOI: 10.1126/science.1207079. eprint: <https://science.sciencemag.org/content/333/6044/888.full.pdf>. URL: <https://science.sciencemag.org/content/333/6044/888>.
- Gurillo, Pedro et al. (2015). "Does tobacco use cause psychosis? Systematic review and meta-analysis". In: *The Lancet Psychiatry* 2.8, pp. 718–725. ISSN: 2215-0366. DOI: [https://doi.org/10.1016/S2215-0366\(15\)00152-2](https://doi.org/10.1016/S2215-0366(15)00152-2). URL: <https://www.sciencedirect.com/science/article/pii/S2215036615001522>.
- Harris, Kenneth D. and Gordon M. G. Shepherd (2015). "The neocortical circuit: themes and variations". In: *Nature Neuroscience* 18.2, pp. 170–181. ISSN: 1546-1726. DOI: 10.1038/nn.3917. URL: <https://doi.org/10.1038/nn.3917>.
- Harris, Kenneth D. and Alexander Thiele (2011). "Cortical state and attention". In: *Nature Reviews Neuroscience* 12.9, pp. 509–523. ISSN: 1471-0048. DOI: 10.1038/nrn3084. URL: <https://doi.org/10.1038/nrn3084>.
- Hartman, Marilyn et al. (2003). "Working memory and schizophrenia: evidence for slowed encoding". In: *Schizophrenia Research* 59.2, pp. 99–113. ISSN: 0920-9964. DOI: [https://doi.org/10.1016/S0920-9964\(01\)00366-8](https://doi.org/10.1016/S0920-9964(01)00366-8). URL: <https://www.sciencedirect.com/science/article/pii/S0920996401003668>.
- Hedrick, Tristan and Jack Waters (2015). "Acetylcholine excites neocortical pyramidal neurons via nicotinic receptors". In: *Journal of Neurophysiology* 113.7. PMID: 25589590, pp. 2195–2209. DOI: 10.1152/jn.00716.2014. eprint: <https://doi.org/10.1152/jn.00716.2014>. URL: <https://doi.org/10.1152/jn.00716.2014>.
- Hill, K. et al. (2004). "Hypofrontality in schizophrenia: a meta-analysis of functional imaging studies". In: *Acta Psychiatrica Scandinavica* 110.4, pp. 243–256. DOI: <https://doi.org/10.1111/j.1600-0447.2004.00376.x>. eprint: <https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1600-0447.2004.00376.x>. URL: <https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1600-0447.2004.00376.x>.
- Holmgren, Carl et al. (2003). "Pyramidal cell communication within local networks in layer 2/3 of rat neocortex". In: *The Journal of Physiology* 551.1, pp. 139–153. DOI: <https://doi.org/10.1111/j.1469-7793.2003.00139.x>. eprint: <https://physoc.onlinelibrary.wiley.com/doi/pdf/10.1111/j.1469-7793.2003.00139.x>. URL: <https://physoc.onlinelibrary.wiley.com/doi/abs/10.1111/j.1469-7793.2003.00139.x>.
- Holt, Gary R. and Christof Koch (July 1997). "Shunting Inhibition Does Not Have a Divisive Effect on Firing Rates*". In: *Neural Computation* 9.5, pp. 1001–1013. ISSN: 0899-7667. DOI: 10.1162/neco.1997.9.5.1001. eprint: <https://direct.mit.edu/neco/article-pdf/9/5/1001/813685/neco.1997.9.5.1001.pdf>. URL: <https://doi.org/10.1162/neco.1997.9.5.1001>.
- Howe, William M. et al. (2010). "Enhancement of Attentional Performance by Selective Stimulation of $\alpha 4\beta 2^*$ nAChRs: Underlying Cholinergic Mechanisms". In: *Neuropsychopharmacology* 35.6, pp. 1391–1401. ISSN: 1740-634X. DOI: 10.1038/npp.2010.9. URL: <https://doi.org/10.1038/npp.2010.9>.
- Howe, William M. et al. (2017). "Acetylcholine Release in Prefrontal Cortex Promotes Gamma Oscillations and Theta–Gamma Coupling during Cue Detection". In: *Journal of Neuroscience* 37.12, pp. 3215–3230. ISSN: 0270-6474. DOI: 10.1523/

- JNEUROSCI. 2737-16. 2017. eprint: <https://www.jneurosci.org/content/37/12/3215.full.pdf>. URL: <https://www.jneurosci.org/content/37/12/3215>.
- Jazbec, Sandra et al. (2007). "Intra-dimensional/extra-dimensional set-shifting performance in schizophrenia: Impact of distractors". In: *Schizophrenia Research* 89.1, pp. 339–349. ISSN: 0920-9964. DOI: <https://doi.org/10.1016/j.schres.2006.08.014>. URL: <https://www.sciencedirect.com/science/article/pii/S092099640600346X>.
- Jiang, Xiaolong et al. (2015). "Principles of connectivity among morphologically defined cell types in adult neocortex". In: *Science* 350.6264. ISSN: 0036-8075. DOI: [10.1126/science.aac9462.full.pdf](https://science.sciencemag.org/content/350/6264/aac9462.full.pdf). eprint: <https://science.sciencemag.org/content/350/6264/aac9462>. URL: <https://science.sciencemag.org/content/350/6264/aac9462>.
- Kamigaki, Tsukasa (2019). "Prefrontal circuit organization for executive control". In: *Neuroscience Research* 140. Circuits and neural dynamics underlying behavior, pp. 23–36. ISSN: 0168-0102. DOI: <https://doi.org/10.1016/j.neures.2018.08.017>. URL: <https://www.sciencedirect.com/science/article/pii/S0168010218304978>.
- Kamigaki, Tsukasa and Yang Dan (2017). "Delay activity of specific prefrontal interneuron subtypes modulates memory-guided behavior". In: *Nature Neuroscience* 20.6, pp. 854–863. ISSN: 1546-1726. DOI: [10.1038/nn.4554](https://doi.org/10.1038/nn.4554). URL: <https://doi.org/10.1038/nn.4554>.
- Kapfer, Christoph et al. (2007). "Supralinear increase of recurrent inhibition during sparse activity in the somatosensory cortex". In: *Nature Neuroscience* 10.6, pp. 743–753. ISSN: 1546-1726. DOI: [10.1038/nn1909](https://doi.org/10.1038/nn1909). URL: <https://doi.org/10.1038/nn1909>.
- Kätsel, Dennis et al. (2011). "The columnar and laminar organization of inhibitory connections to neocortical excitatory cells". In: *Nature Neuroscience* 14.1, pp. 100–107. ISSN: 1546-1726. DOI: [10.1038/nn.2687](https://doi.org/10.1038/nn.2687). URL: <https://doi.org/10.1038/nn.2687>.
- Kim, Dohoung et al. (2016). "Distinct Roles of Parvalbumin- and Somatostatin-Expressing Interneurons in Working Memory". In: *Neuron* 92.4, pp. 902–915. ISSN: 0896-6273. DOI: <https://doi.org/10.1016/j.neuron.2016.09.023>. URL: <https://www.sciencedirect.com/science/article/pii/S0896627316305827>.
- Kim, Yongsoo et al. (2017). "Brain-wide Maps Reveal Stereotyped Cell-Type-Based Cortical Architecture and Subcortical Sexual Dimorphism". In: *Cell* 171.2, 456–469.e22. ISSN: 0092-8674. DOI: <https://doi.org/10.1016/j.cell.2017.09.020>. URL: <https://www.sciencedirect.com/science/article/pii/S0092867417310693>.
- Kleykamp, Bethea A. et al. (2005). "The Effects of Nicotine on Attention and Working Memory in Never-Smokers." In: *Psychology of Addictive Behaviors* 19.4, pp. 433–438. DOI: [10.1037/0893-164X.19.4.433](https://doi.org/10.1037/0893-164X.19.4.433). URL: <https://doi.org/10.1037/0893-164X.19.4.433>.
- Kolluri, Nutan et al. (2005). "Lamina-Specific Reductions in Dendritic Spine Density in the Prefrontal Cortex of Subjects With Schizophrenia". In: *American Journal of Psychiatry* 162.6. PMID: 15930070, pp. 1200–1202. DOI: [10.1176/appi.ajp.162.6.1200](https://doi.org/10.1176/appi.ajp.162.6.1200). eprint: <https://doi.org/10.1176/appi.ajp.162.6.1200>. URL: <https://doi.org/10.1176/appi.ajp.162.6.1200>.
- Koukouli, Fani, Marie Rooy, and Uwe Maskos (2016). "Early and progressive deficit of neuronal activity patterns in a model of local amyloid pathology in mouse prefrontal cortex". eng. In: *Aging* 8.12. 27999185[pmid], pp. 3430–3449. ISSN: 1945-4589. URL: <https://pubmed.ncbi.nlm.nih.gov/27999185>.

- Koukouli, Fani et al. (2016). "Nicotinic receptors in mouse prefrontal cortex modulate ultraslow fluctuations related to conscious processing". In: *Proceedings of the National Academy of Sciences* 113.51, pp. 14823–14828. ISSN: 0027-8424. DOI: 10.1073/pnas.1614417113. eprint: <https://www.pnas.org/content/113/51/14823.full.pdf>. URL: <https://www.pnas.org/content/113/51/14823>.
- Koukouli, Fani et al. (2017). "Nicotine reverses hypofrontality in animal models of addiction and schizophrenia". In: *Nature Medicine* 23.3, pp. 347–354. ISSN: 1546-170X. DOI: 10.1038/nm.4274. URL: <https://doi.org/10.1038/nm.4274>.
- Krishnamurthy, Pradeep, Gilad Silberberg, and Anders Lansner (Apr. 2012). "A Cortical Attractor Network with Martinotti Cells Driven by Facilitating Synapses". In: *PLOS ONE* 7.4, pp. 1–12. DOI: 10.1371/journal.pone.0030752. URL: <https://doi.org/10.1371/journal.pone.0030752>.
- Kruglikov, Illya and Bernardo Rudy (2008). "Perisomatic GABA Release and Thalamocortical Integration onto Neocortical Excitatory Cells Are Regulated by Neuromodulators". In: *Neuron* 58.6, pp. 911–924. ISSN: 0896-6273. DOI: <https://doi.org/10.1016/j.neuron.2008.04.024>. URL: <https://www.sciencedirect.com/science/article/pii/S0896627308003784>.
- Lagler, Michael et al. (2016). "Divisions of Identified Parvalbumin-Expressing Basket Cells during Working Memory-Guided Decision Making". In: *Neuron* 91.6, pp. 1390–1401. ISSN: 0896-6273. DOI: <https://doi.org/10.1016/j.neuron.2016.08.010>. URL: <https://www.sciencedirect.com/science/article/pii/S0896627316305025>.
- Lawrence, Natalia S, Thomas J Ross, and Elliot A Stein (2002). "Cognitive Mechanisms of Nicotine on Visual Attention". In: *Neuron* 36.3, pp. 539–548. ISSN: 0896-6273. DOI: [https://doi.org/10.1016/S0896-6273\(02\)01004-8](https://doi.org/10.1016/S0896-6273(02)01004-8). URL: <https://www.sciencedirect.com/science/article/pii/S0896627302010048>.
- Lee, Junghee and Sohee Park (2005). "Working Memory Impairments in Schizophrenia: A Meta-Analysis." In: *Journal of Abnormal Psychology* 114.4, pp. 599–611. DOI: 10.1037/0021-843X.114.4.599. URL: <https://doi.org/10.1037/0021-843X.114.4.599>.
- Lewis, David A., Takanori Hashimoto, and David W. Volk (2005). "Cortical inhibitory neurons and schizophrenia". In: *Nature Reviews Neuroscience* 6.4, pp. 312–324. ISSN: 1471-0048. DOI: 10.1038/nrn1648. URL: <https://doi.org/10.1038/nrn1648>.
- Lin, Shih-Chieh and Miguel A.L. Nicolelis (2008). "Neuronal Ensemble Bursting in the Basal Forebrain Encodes Salience Irrespective of Valence". In: *Neuron* 59.1, pp. 138–149. ISSN: 0896-6273. DOI: <https://doi.org/10.1016/j.neuron.2008.04.031>. URL: <https://www.sciencedirect.com/science/article/pii/S0896627308004091>.
- Lombardo, Sylvia and Uwe Maskos (2015). "Role of the nicotinic acetylcholine receptor in Alzheimer's disease pathology and treatment". In: *Neuropharmacology* 96. The Nicotinic Acetylcholine Receptor: From Molecular Biology to Cognition, pp. 255–262. ISSN: 0028-3908. DOI: <https://doi.org/10.1016/j.neuropharm.2014.11.018>. URL: <https://www.sciencedirect.com/science/article/pii/S0028390814004341>.
- Mirza, N. R. and Ian P. Stolerman (1998). "Nicotine enhances sustained attention in the rat under specific task conditions". In: *Psychopharmacology* 138.3, pp. 266–274. ISSN: 1432-2072. DOI: 10.1007/s002130050671. URL: <https://doi.org/10.1007/s002130050671>.
- Mongillo, Gianluigi, Omri Barak, and Misha Tsodyks (2008). "Synaptic Theory of Working Memory". In: *Science* 319.5869, pp. 1543–1546. ISSN: 0036-8075. DOI: 10.

- 1126/science.1150769. eprint: <https://science.scienmag.org/content/319/5869/1543.full.pdf>. URL: <https://science.scienmag.org/content/319/5869/1543>.
- Moutard, Clément, Stanislas Dehaene, and Rafael Malach (2015). "Spontaneous Fluctuations and Non-linear Ignitions: Two Dynamic Faces of Cortical Recurrent Loops". In: *Neuron* 88.1, pp. 194–206. ISSN: 0896-6273. DOI: <https://doi.org/10.1016/j.neuron.2015.09.018>. URL: <https://www.sciencedirect.com/science/article/pii/S0896627315007758>.
- Mucke, Lennart (2009). "Alzheimer's disease". In: *Nature* 461.7266, pp. 895–897. ISSN: 1476-4687. DOI: [10.1038/461895a](https://doi.org/10.1038/461895a). URL: <https://doi.org/10.1038/461895a>.
- Murray, Andrew J. et al. (2015). "Parvalbumin-positive interneurons of the prefrontal cortex support working memory and cognitive flexibility". In: *Scientific Reports* 5.1, p. 16778. ISSN: 2045-2322. DOI: [10.1038/srep16778](https://doi.org/10.1038/srep16778). URL: <https://doi.org/10.1038/srep16778>.
- Obermayer, Joshua et al. (2018). "Lateral inhibition by Martinotti interneurons is facilitated by cholinergic inputs in human and mouse neocortex". In: *Nature Communications* 9.1, p. 4101. ISSN: 2041-1723. DOI: [10.1038/s41467-018-06628-w](https://doi.org/10.1038/s41467-018-06628-w). URL: <https://doi.org/10.1038/s41467-018-06628-w>.
- Papasavvas, Christoforos A. et al. (2015). "Gain control through divisive inhibition prevents abrupt transition to chaos in a neural mass model". In: *Phys. Rev. E* 92 (3), p. 032723. DOI: [10.1103/PhysRevE.92.032723](https://doi.org/10.1103/PhysRevE.92.032723). URL: <https://link.aps.org/doi/10.1103/PhysRevE.92.032723>.
- Papasavvas, Christoforos A. et al. (2020). "Divisive gain modulation enables flexible and rapid entrainment in a neocortical microcircuit model". In: *Journal of Neurophysiology* 123.3. PMID: 32023140, pp. 1133–1143. DOI: [10.1152/jn.00401.2019](https://doi.org/10.1152/jn.00401.2019). eprint: <https://doi.org/10.1152/jn.00401.2019>. URL: <https://doi.org/10.1152/jn.00401.2019>.
- Parikh, Vinay et al. (2007). "Prefrontal Acetylcholine Release Controls Cue Detection on Multiple Timescales". In: *Neuron* 56.1, pp. 141–154. ISSN: 0896-6273. DOI: <https://doi.org/10.1016/j.neuron.2007.08.025>. URL: <https://www.sciencedirect.com/science/article/pii/S0896627307006745>.
- Parikh, Vinay et al. (2008). "Glutamatergic Contributions to Nicotinic Acetylcholine Receptor Agonist-Evoked Cholinergic Transients in the Prefrontal Cortex". In: *Journal of Neuroscience* 28.14, pp. 3769–3780. ISSN: 0270-6474. DOI: [10.1523/JNEUROSCI.5251-07.2008](https://doi.org/10.1523/JNEUROSCI.5251-07.2008). eprint: <https://www.jneurosci.org/content/28/14/3769.full.pdf>. URL: <https://www.jneurosci.org/content/28/14/3769>.
- Parikh, Vinay et al. (2010). "Prefrontal 2 Subunit-Containing and 7 Nicotinic Acetylcholine Receptors Differentially Control Glutamatergic and Cholinergic Signaling". In: *Journal of Neuroscience* 30.9, pp. 3518–3530. ISSN: 0270-6474. DOI: [10.1523/JNEUROSCI.5712-09.2010](https://doi.org/10.1523/JNEUROSCI.5712-09.2010). eprint: <https://www.jneurosci.org/content/30/9/3518.full.pdf>. URL: <https://www.jneurosci.org/content/30/9/3518>.
- Park, Sohee and Philip S. Holzman (Dec. 1992). "Schizophrenics Show Spatial Working Memory Deficits". In: *Archives of General Psychiatry* 49.12, pp. 975–982. ISSN: 0003-990X. DOI: [10.1001/archpsyc.1992.01820120063009](https://doi.org/10.1001/archpsyc.1992.01820120063009). eprint: https://jamanetwork.com/journals/jamapsychiatry/articlepdf/495979/archpsyc\49_12_009.pdf. URL: <https://doi.org/10.1001/archpsyc.1992.01820120063009>.
- Park, Sohee et al. (2000). "Nicotine Impairs Spatial Working Memory while Leaving Spatial Attention Intact". In: *Neuropsychopharmacology* 22.2, pp. 200–209. ISSN: 1740-634X. DOI: [10.1016/S0893-133X\(99\)00098-6](https://doi.org/10.1016/S0893-133X(99)00098-6). URL: [https://doi.org/10.1016/S0893-133X\(99\)00098-6](https://doi.org/10.1016/S0893-133X(99)00098-6).

- Pfeffer, Carsten K. et al. (2013). "Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons". In: *Nature Neuroscience* 16.8, pp. 1068–1076. ISSN: 1546-1726. DOI: [10.1038/nn.3446](https://doi.org/10.1038/nn.3446). URL: <https://doi.org/10.1038/nn.3446>.
- Pi, Hyun-Jae et al. (2013). "Cortical interneurons that specialize in disinhibitory control". In: *Nature* 503.7477, pp. 521–524. ISSN: 1476-4687. DOI: [10.1038/nature12676](https://doi.org/10.1038/nature12676). URL: <https://doi.org/10.1038/nature12676>.
- Poorthuis, Rogier B. et al. (Jan. 2012). "Layer-Specific Modulation of the Prefrontal Cortex by Nicotinic Acetylcholine Receptors". In: *Cerebral Cortex* 23.1, pp. 148–161. ISSN: 1047-3211. DOI: [10.1093/cercor/bhr390](https://doi.org/10.1093/cercor/bhr390). eprint: <https://academic.oup.com/cercor/article-pdf/23/1/148/17307116/bhr390.pdf>. URL: <https://doi.org/10.1093/cercor/bhr390>.
- Porter, James T. et al. (1999). "Selective Excitation of Subtypes of Neocortical Interneurons by Nicotinic Receptors". In: *Journal of Neuroscience* 19.13, pp. 5228–5235. ISSN: 0270-6474. DOI: [10.1523/JNEUROSCI.19-13-05228.1999](https://doi.org/10.1523/JNEUROSCI.19-13-05228.1999). eprint: <https://www.jneurosci.org/content/19/13/5228.full.pdf>. URL: <https://www.jneurosci.org/content/19/13/5228>.
- Povysheva, Nadezhda V. et al. (Aug. 2013). "Electrophysiological Heterogeneity of Fast-Spiking Interneurons: Chandelier versus Basket Cells". In: *PLOS ONE* 8.8, pp. 1–13. DOI: [10.1371/journal.pone.0070553](https://doi.org/10.1371/journal.pone.0070553). URL: <https://doi.org/10.1371/journal.pone.0070553>.
- Psychiatric Genomics Consortium, Schizophrenia Working Group of the (2014). "Biological insights from 108 schizophrenia-associated genetic loci". eng. In: *Nature* 511.7510. 25056061[pmid], pp. 421–427. ISSN: 1476-4687. DOI: [10.1038/nature13595](https://doi.org/10.1038/nature13595). URL: <https://pubmed.ncbi.nlm.nih.gov/25056061>.
- Rao, Srinivas G., Graham V. Williams, and Patricia S. Goldman-Rakic (1999). "Isodirectional Tuning of Adjacent Interneurons and Pyramidal Cells During Working Memory: Evidence for Microcolumnar Organization in PFC". In: *Journal of Neurophysiology* 81.4. PMID: 10200225, pp. 1903–1916. DOI: [10.1152/jn.1999.81.4.1903](https://doi.org/10.1152/jn.1999.81.4.1903). eprint: <https://doi.org/10.1152/jn.1999.81.4.1903>. URL: <https://doi.org/10.1152/jn.1999.81.4.1903>.
- (2000). "Destruction and Creation of Spatial Tuning by Disinhibition: GABA_A Blockade of Prefrontal Cortical Neurons Engaged by Working Memory". In: *Journal of Neuroscience* 20.1, pp. 485–494. ISSN: 0270-6474. DOI: [10.1523/JNEUROSCI.20-01-00485.2000](https://doi.org/10.1523/JNEUROSCI.20-01-00485.2000). eprint: <https://www.jneurosci.org/content/20/1/485.full.pdf>. URL: <https://www.jneurosci.org/content/20/1/485>.
- Rezvani, Amir H and Edward D Levin (2001). "Cognitive effects of nicotine". In: *Biological Psychiatry* 49.3. Nicotine Mechanisms in Alzheimer's Disease, pp. 258–267. ISSN: 0006-3223. DOI: [https://doi.org/10.1016/S0006-3223\(00\)01094-5](https://doi.org/10.1016/S0006-3223(00)01094-5). URL: <https://www.sciencedirect.com/science/article/pii/S0006322300010945>.
- Rooy, Marie et al. (2021). "Cholinergic modulation of hierarchical inhibitory control over cortical resting state dynamics: Local circuit modeling of schizophrenia-related hypofrontality". In: *Current Research in Neurobiology* 2, p. 100018. ISSN: 2665-945X. DOI: <https://doi.org/10.1016/j.crneur.2021.100018>. URL: <https://www.sciencedirect.com/science/article/pii/S2665945X21000140>.
- Roux, Lisa and György Buzsáki (2015). "Tasks for inhibitory interneurons in intact brain circuits". In: *Neuropharmacology* 88. GABAergic Signaling in Health and Disease, pp. 10–23. ISSN: 0028-3908. DOI: <https://doi.org/10.1016/j.neuropharm.2014.09.011>. URL: <https://www.sciencedirect.com/science/article/pii/S0028390814003189>.

- Sacco, Kristi A. et al. (June 2005). "Effects of Cigarette Smoking on Spatial Working Memory and Attentional Deficits in Schizophrenia: Involvement of Nicotinic Receptor Mechanisms". In: *Archives of General Psychiatry* 62.6, pp. 649–659. ISSN: 0003-990X. DOI: [10.1001/archpsyc.62.6.649](https://doi.org/10.1001/archpsyc.62.6.649). eprint: <https://jamanetwork.com/journals/jamapsychiatry/articlepdf/208660/yoa40240.pdf>. URL: <https://doi.org/10.1001/archpsyc.62.6.649>.
- Sahakian, BARBARA J. et al. (June 1988). "A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease". In: *Brain* 111.3, pp. 695–718. ISSN: 0006-8950. DOI: [10.1093/brain/111.3.695](https://doi.org/10.1093/brain/111.3.695). eprint: <https://academic.oup.com/brain/article-pdf/111/3/695/846357/111-3-695.pdf>. URL: <https://doi.org/10.1093/brain/111.3.695>.
- Sanchez-Vives, Maria V. and David A. McCormick (2000). "Cellular and network mechanisms of rhythmic recurrent activity in neocortex". In: *Nature Neuroscience* 3.10, pp. 1027–1034. ISSN: 1546-1726. DOI: [10.1038/79848](https://doi.org/10.1038/79848). URL: <https://doi.org/10.1038/79848>.
- Sarter, Martin and Cindy Lustig (2019). "Cholinergic double duty: cue detection and attentional control". In: *Current Opinion in Psychology* 29. Attention Perception, pp. 102–107. ISSN: 2352-250X. DOI: <https://doi.org/10.1016/j.copsyc.2018.12.026>. URL: <https://www.sciencedirect.com/science/article/pii/S2352250X18301623>.
- Smucny, Jason et al. (2013). "Early sensory processing deficits predict sensitivity to distraction in schizophrenia". In: *Schizophrenia Research* 147.1, pp. 196–200. ISSN: 0920-9964. DOI: <https://doi.org/10.1016/j.schres.2013.03.025>. URL: <https://www.sciencedirect.com/science/article/pii/S0920996413001710>.
- Staresina, Bernhard P. et al. (2015). "Hierarchical nesting of slow oscillations, spindles and ripples in the human hippocampus during sleep". In: *Nature Neuroscience* 18.11, pp. 1679–1686. ISSN: 1546-1726. DOI: [10.1038/nn.4119](https://doi.org/10.1038/nn.4119). URL: <https://doi.org/10.1038/nn.4119>.
- Sun, Yongan et al. (2017). "Nicotinic 42 Cholinergic Receptor Influences on Dorsolateral Prefrontal Cortical Neuronal Firing during a Working Memory Task". In: *Journal of Neuroscience* 37.21, pp. 5366–5377. ISSN: 0270-6474. DOI: [10.1523/JNEUROSCI.0364-17.2017](https://doi.org/10.1523/JNEUROSCI.0364-17.2017). eprint: <https://www.jneurosci.org/content/37/21/5366.full.pdf>. URL: <https://www.jneurosci.org/content/37/21/5366>.
- Tobacco and Genetics Consortium (2010). "Genome-wide meta-analyses identify multiple loci associated with smoking behavior". eng. In: *Nature genetics* 42.5. 20418890[pmid], pp. 441–447. ISSN: 1546-1718. DOI: [10.1038/ng.571](https://doi.org/10.1038/ng.571). URL: <https://pubmed.ncbi.nlm.nih.gov/20418890>.
- Tremblay, Robin, Soohyun Lee, and Bernardo Rudy (2016). "GABAergic Interneurons in the Neocortex: From Cellular Properties to Circuits". In: *Neuron* 91.2, pp. 260–292. ISSN: 0896-6273. DOI: <https://doi.org/10.1016/j.neuron.2016.06.033>. URL: <https://www.sciencedirect.com/science/article/pii/S0896627316303117>.
- Uylings, Harry B.M., Henk J. Groenewegen, and Bryan Kolb (2003). "Do rats have a prefrontal cortex?" In: *Behavioural Brain Research* 146.1. The Rodent Prefrontal Cortex, pp. 3–17. ISSN: 0166-4328. DOI: <https://doi.org/10.1016/j.bbr.2003.09.028>. URL: <https://www.sciencedirect.com/science/article/pii/S0166432803003346>.
- Vyazovskiy, Vladyslav V. and Kenneth D. Harris (2013). "Sleep and the single neuron: the role of global slow oscillations in individual cell rest". In: *Nature Reviews Neuroscience* 14.6, pp. 443–451. ISSN: 1471-0048. DOI: [10.1038/nrn3494](https://doi.org/10.1038/nrn3494). URL: <https://doi.org/10.1038/nrn3494>.

- Wang, X.-J. et al. (2004). "Division of labor among distinct subtypes of inhibitory neurons in a cortical microcircuit of working memory". In: *Proceedings of the National Academy of Sciences* 101.5, pp. 1368–1373. ISSN: 0027-8424. DOI: 10.1073/pnas.0305337101. eprint: <https://www.pnas.org/content/101/5/1368.full.pdf>. URL: <https://www.pnas.org/content/101/5/1368>.
- Wang, Xiao-Jing (2001). "Synaptic reverberation underlying mnemonic persistent activity". In: *Trends in Neurosciences* 24.8, pp. 455–463. ISSN: 0166-2236. DOI: [https://doi.org/10.1016/S0166-2236\(00\)01868-3](https://doi.org/10.1016/S0166-2236(00)01868-3). URL: <https://www.sciencedirect.com/science/article/pii/S0166223600018683>.
- Wester, Jason C. and Diego Contreras (2012). "Columnar Interactions Determine Horizontal Propagation of Recurrent Network Activity in Neocortex". In: *Journal of Neuroscience* 32.16, pp. 5454–5471. ISSN: 0270-6474. DOI: 10.1523/JNEUROSCI.5006-11.2012. eprint: <https://www.jneurosci.org/content/32/16/5454.full.pdf>. URL: <https://www.jneurosci.org/content/32/16/5454>.
- Wilson, Hugh R. and Jack D. Cowan (1972). "Excitatory and Inhibitory Interactions in Localized Populations of Model Neurons". In: *Biophysical Journal* 12.1, pp. 1–24. ISSN: 0006-3495. DOI: [https://doi.org/10.1016/S0006-3495\(72\)86068-5](https://doi.org/10.1016/S0006-3495(72)86068-5). URL: <https://www.sciencedirect.com/science/article/pii/S0006349572860685>.
- Winterer, Georg et al. (2010). "Risk gene variants for nicotine dependence in the CHRNA5–CHRNA3–CHRNB4 cluster are associated with cognitive performance". In: *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 153B.8, pp. 1448–1458. DOI: <https://doi.org/10.1002/ajmg.b.31126>. eprint: <https://onlinelibrary.wiley.com/doi/pdf/10.1002/ajmg.b.31126>. URL: <https://onlinelibrary.wiley.com/doi/abs/10.1002/ajmg.b.31126>.
- Yang, Yang et al. (2013). "Nicotinic 7 receptors enhance NMDA cognitive circuits in dorsolateral prefrontal cortex". In: *Proceedings of the National Academy of Sciences* 110.29, pp. 12078–12083. ISSN: 0027-8424. DOI: 10.1073/pnas.1307849110. eprint: <https://www.pnas.org/content/110/29/12078.full.pdf>. URL: <https://www.pnas.org/content/110/29/12078>.
- Yang, Zhilai et al. (2018). "The Changes of Intrinsic Excitability of Pyramidal Neurons in Anterior Cingulate Cortex in Neuropathic Pain". In: *Frontiers in Cellular Neuroscience* 12, p. 436. ISSN: 1662-5102. DOI: 10.3389/fncel.2018.00436. URL: <https://www.frontiersin.org/article/10.3389/fncel.2018.00436>.
- Yavorska, Iryna and Michael Wehr (2016). "Somatostatin-Expressing Inhibitory Interneurons in Cortical Circuits". In: *Frontiers in Neural Circuits* 10, p. 76. ISSN: 1662-5110. DOI: 10.3389/fncir.2016.00076. URL: <https://www.frontiersin.org/article/10.3389/fncir.2016.00076>.
- Zaitsev, A. V. and D. A. Lewis (2013). "Functional properties and short-term dynamics of unidirectional and reciprocal synaptic connections between layer 2/3 pyramidal cells and fast-spiking interneurons in juvenile rat prefrontal cortex". In: *European Journal of Neuroscience* 38.7, pp. 2988–2998. DOI: <https://doi.org/10.1111/ejn.12294>. eprint: <https://onlinelibrary.wiley.com/doi/pdf/10.1111/ejn.12294>. URL: <https://onlinelibrary.wiley.com/doi/abs/10.1111/ejn.12294>.