Chapter 5
Modeling the Effects of Modafinil on Selective Attention Electroencephalographic Neural Correlates

Carlos Trenado

Abstract Nowadays, the development of pharmaceutical neuroenhancers attracts considerable attention due to their applicability and controversial implications within human society. Modafinil is one such neurorenhancer that has gained notoriety due to its widespread use in military and college environments. Several studies in the field of cognitive neuroscience, psychophysics and pharmacology have reported on the human brain differential processing under the influence of modafinil. Unfortunately, the underlying mechanisms by which modafinil modulates excitatory and inhibitory neural populations on cortical and subcortical neural networks as well as its positive or negative effects are not well understood. To cope with this, we propose a biologically-inspired, large-scale computational model for studying modafinil effects on electroencephalographic neural correlates of attention. Numerical simulations are performed and reconciled with recent experimental findings on the influence of modafinil on the locus coeruleus (LC) and the corticothalamic pathways. It is concluded that neural computational models represent a promising approach to gain insight into the neurodynamics of cognitive neuroenhancers.

Keywords Neuroenhancement • Modafinil • Mathematical modeling • Neurodynamics • Electroencephalography

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5.1 Outline

The present chapter introduces for the first time computational modeling results on the effect of modafinil on electroencephalographic attention neural correlates based on the hypothesis that modafinil modulates neural activity in the locus coeruleus. Notably, such a modulation has been implicated with an enhancement in connectivity between the prefrontal cortex and subcortical structures as in the case of the thalamus and the limbic system. The organization of this chapter is as follows: Sect. 5.2 introduces the basics about modafinil and the emerging field of neural enhancement modeling; Sect. 5.3 presents our biologically-inspired model of modafinil effects on electroencephalographic correlates of selective attention; Sect. 5.4 introduces our numerical results; Sect. 5.5 presents our conclusions.

5.2 Introduction

5.2.1 Modafinil

Modafinil is a psychostimulant that has been utilized to enhance wakefulness, attention capacity, and vigilance (Franke and Lieb 2010). It has attracted considerable interest due to its pharmacological profile that differs from traditional neuroenhancers such as amphetamines and methylphenidate. Several research studies support that modafinil is a safe, well-tolerated drug, with long-lasting effects (Sugarman et al. 2011). In fact, modafinil has been tested in the treatment of Alzheimer's disease (Bransfield 2004); depression (Frye et al. 2007); attention-deficit hyperactivity disorder (ADHD) (Keen and Hadijikoumi 2011); multiple sclerosis-induced fatigue (Téllez and Montalbán 2004; Nicholas and Chataway 2007); post-cognitive impairment in schizophrenia (Ballon and Feifel 2006; Henderson et al. 2005); spasticity associated with cerebral palsy (Ballon and Feifel 2006); age-related memory decline as a neuroprotective agent against the "dopamine-deficiency disorder" Parkinson's disease (Knie et al. 2011; van Vliet et al. 2006) and the treatment of cancer-related fatigue (Morrow et al. 2005). The use of modafinil in the treatment of shift work sleep disorder and obstructive sleep apnea has also been emphasized (Ballon and Feifel 2006). Focusing on arousal enhancement, modafinil has gained widespread attention in popular press articles because of its increasing popularity among students at leading American colleges and military personnel.

In spite of the aforementioned potential curative benefits, concerns about possible side effects related to modafinil consumption have also been expressed by several authors, who advocate limitations on its daily use; these authors' concerns are based on the fact that there is a lack of knowledge regarding modafinil's neural mechanisms and the way it influences brain structures (Joos et al. 2010).

With regard to neural mechanisms, some authors hypothesized that modafinil promotes wakefulness via its effects in the anterior hypothalamus, whereas a

dopamine-related action in the nucleus accumbens has been considered moderate (Scamell et al. 2000). With respect to alertness and partial wakefulness, it has been assumed that modafinil inhibits the reuptake of noradrenaline by the noradren-ergic terminals on sleep-promoting neurons of the ventrolateral preoptic nucleus (VLPO) (Gallopin et al. 2004). More significant, perhaps, has been the report of modafinil's ability to increase excitatory glutamatergic transmission in thalamic and limbic structures. This mechanism reduces local GABAergic transmission, thereby diminishing GABA (A) receptor signaling on the mesolimbic and thalamic dopamine terminals (Ferraro et al. 1997). With regard to attentional control, recent studies have stressed the importance of the locus coeruleus (LC), a portion of the brainstem. It has been hypothesized that the LC is involved in shifts from distractible to attentive states. By visualizing activity from functional magnetic resonance imaging (fMRI), researchers have shown that modafinil indeed alters the state of the LC (Minzenberg et al. 2008). Moreover, these authors were able to shift subjects into a more attentive state by administering modafinil, as reflected by enhanced coordinated brain activity and better performance on an attentional test. In particular, the reported experimental findings suggest that modafinil decreases activity in the LC while favoring subcortical connectivity with the prefrontal cortex.

5.2.2 Neural Enhancement Modeling

Modeling, in the most abstract sense, provides a conceptual structure by which assumptions are incorporated and hypotheses articulated. A mathematical model differs from a theoretical, descriptive model in that the assumptions are articulated via mathematical rules. In particular, mathematical modeling is intended not only to describe, explain and test hypotheses about real-world phenomena arising from fields such as engineering, physics, physiology ecology, neuroscience, wildlife management, chemistry, economics, etc. but, more importantly, to make predictions. In particular, neural modeling addresses the proposal and development of compu-tational and mathematical schemes aimed to study the human brain function. Due to the brain's high complexity (the brain involves a large number of interconnected neurons underlying responses at different temporal and spatial scales), a modeling approach represents a plausible methodology for describing and extracting relevant features of the brain's functionality in a tractable and reduced manner.

In order to successfully model and elucidate the neurodynamics of prospective neuroenhancers such as modafinil, one should consider the multiscale nature of the human brain. Theoretically, neuroenhancement modeling is achieved by integrating responses of neural populations into large scale neural responses that are comparable to data normally obtained by way of experimental techniques. Such modeling formulations have already proven their capability for capturing details ranging from single neurons to neural networks and cortical column maps. Such models, might in principle, provide deeper insights into the influence of neuroenhancers at neural network and cortical levels. In order to test prospective functional mechanisms

of pharmaceutical neuroenhancers, the multiscale modeling approaches enable the integration of spatial (fMRI data, optogenetics, voltage sensitive dye imaging) and temporal data (behavioral studies, electroencephalographic data and intracranial recordings) from current brain imaging technologies.

In addition, implementing an efficient and validated model for studying the dynamics of brain structures under the influence of a specific psychostimulant, could be useful not only for developing better cognitive enhancers, but also for supporting the development of diagnostic tools and treatments for people suffering from a variety of neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD), autism, schizophrenia, etc.

5.3 Computational Model

The proposed model is a biologically plausible, large-scale, computational model, whose architecture and connectivity adopt principles from brain cortical and subcortical structures (Trenado et al. 2009). In particular, the model incorporates excitatory and inhibitory neural population effects that correspond to neural networks at the cortex, the thalamus, and the limbic system. Modulatory effects of modafinil are thus incorporated by a "modafinil protocol" block that regulates activity in the locus coeruleus (LC) (see Fig. 5.1). The critical role of the interaction between the cortex, the thalamus and the limbic system in relation to control and gating
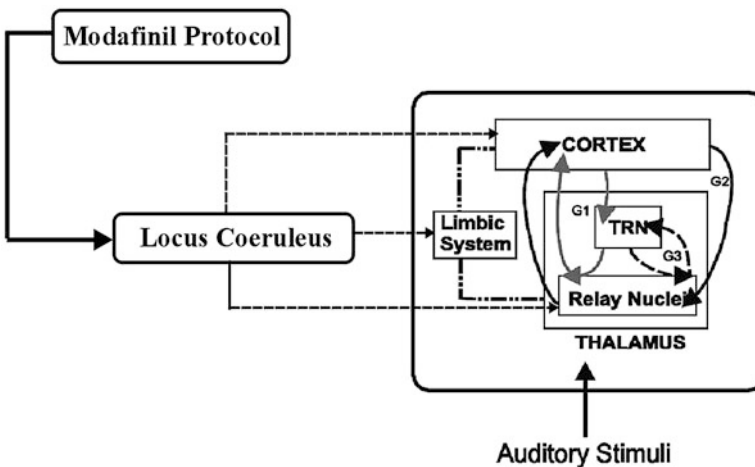

Fig. 5.1 Scheme of the brain structures considered in the model for studying modafinil effects on neural correlates of selective attention. The modafinil protocol block refers to a dose of modafinil being administered to a patient or subject; the locus coeruleus block (*LC*) represents the mean neural activity at that structure, which in turn influences the limbic system and corticothalamic connectivity

of selective attention has already been addressed by several authors (Ledoux et al. 1991; Destexhe 2000); whereas, the involvement of the LC in relation to modafinil has just recently been addressed (Minzenberg et al. 2008).

Interestingly, the LC, a small nucleus located in the pons, represents the main source of noradrenaline in the forebrain. In addition, the LC is involved in what is known as the ascending reticular activating system, a neural path critical for arousal and wakefulness. Specifically, LC neurons possess wide projections and their activity varies according to the degree of arousal and specific cognitive processes. A crucial observation is that the variability in LC neural responses results in a release of noradrenaline that targets numerous brain areas including the human prefrontal cortex (Bouret and Sara 2005).

As suggested by some authors (Minzenberg et al. 2008), we assume that modafinil acts by decreasing the neural activity in the LC, while enhancing neural activity between cortical and prominent subcortical structures. In this regard, we propose a relationship between modafinil dose (D) (typical range of dose 0–400 mg) and the LC neural activity (LCN) as provided by

$$LCN = \exp(-\theta D + K) \tag{5.1}$$

where θ denotes a parameter governing the degree of decay of LCN activity and K is a threshold determined by the minimum level of LCN activity.

With respect to thalamic modulation, we propose a relationship between corticothalamic gains G_1 and G_2 and the LCN activity as provided by,

$$\Psi = \exp(-(LCN)^2)$$
$$\Psi = G_1 + G_2 \tag{5.2}$$

Here, the values of parameters G_1 and G_2 are selected in accordance with Trenado et al. (2009).

In our model, consideration of excitatory and inhibitory neural activities from both cortical and subcortical populations (Fig. 5.2) is achieved by means of a mean field equation of the form,

$$P_a = N_{ae}s_e\phi_e + N_{ai}s_i\phi_i + N_{as}s_s\phi_s$$

where ϕ_e, ϕ_i and ϕ_s denote mean field excitatory, inhibitory and subcortical neural activities, and N_{ae}, N_{ai}, N_{as} denote parameters related to excitatory, inhibitory and subcortical connectivity of neural populations.

The computation of the mean soma potential V_a is performed by integrating neural activities from different neural populations as provided by the following equation,

$$V_a(\vec{r}, t) = \int_{-\infty}^{\infty} L(t - t')P_a(\vec{r}, t')dt'$$

Fig. 5.2 The figure shows schematically the interaction and integration of cortical and subcortical neural populations which are summarized by the term (P_a)
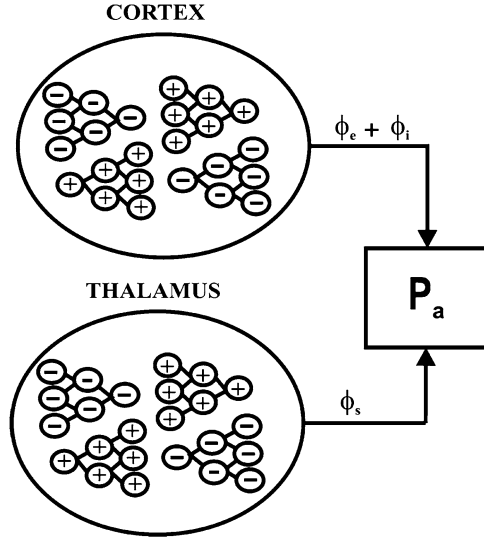
The term L accounts for low-pass dendritic effects. Here, the mean firing rate is defined by a sigmoidal type function; the propagation of action potentials is accounted for by a damped wave equation; whereas, corticothalamic modulation is modeled by means of a transfer function involving gains G_1, G_2 and G_3 (see Trenado et al. 2009 for details).

5.4 Numerical Results

By specifying a modafinil protocol (namely, by defining a relationship between modafinil doses administered to a subject and the degree of LC activity, Eq. (5.1)), we are able to carry out the modulation of mean neural activity of LC neurons. Subsequently, cortical and subcortical modulation is achieved by varying gains G_1 and G_2 under the influence of LC neuron activity as specified by Eq. (5.2). In particular, numerical simulation of neural correlates of selective attention as reflected by the degree of synchronization of relevant evoked response components N1 (occurring at ∼100 ms) and P2 (occurring at ∼200 ms), was performed by following the approach in Trenado et al. (2009). Figure 5.3 shows numerical results of the N1 component synchronization by varying LC neural activity. In agreement with our simulations and the results reported in Minzenberg et al. (2008), it was observed that a high synchronization of the N1 component corresponded to a low LC neural activity; whereas, a high activity of the LC led to a decrease in the synchronization of the N1 component. As suggested by Trenado et al. (2009) and Bollimunta (2011), varying parameters G_1 and G_2 reflects a modulation of corticothalamic circuits that has implications on a mechanism for selective attention.
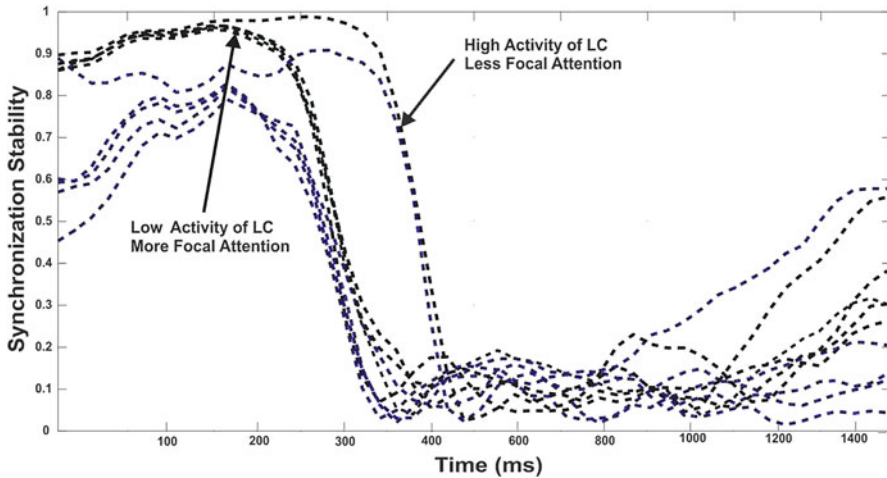
Fig. 5.3 Shows synchronization results of relevant evoked response components by varying LC neural activity. Here, a coherent synchronization corresponds to a state of focal attention, while a decrease in synchronization corresponds to a state of non-focal attention

Thus, our simulations provide support for the hypothesis that an increase (decrease) in LC neural activity leads to a non-focal (focal) attention state. In light of previous studies on neural correlates of selective attention, an observed synchronization (desynchronization) of the N1 component has been interpreted as intensification (relaxation) of the activity of the thalamic relay nuclei that leads to an increasing (decreasing) allocation of brain resources towards a target stimulus.

5.5   Conclusions

While the present study is preliminary, the obtained results showed the potential of applying neural computational models to test different hypotheses regarding the influence of neuroenhancers on humans. The present chapter addresses, for the first time, the effects of modafinil on a corticothalamic large-scale model of neural correlates of selective attention. In particular, the model is useful to test recent experimental findings regarding the involvement of the LC neural activity and its role in facilitating bottom-up projections thus enabling improvement in focal attention (Fig. 5.3). An interesting feature that is yet to be explored is the transition between states of focal and non-focal attention under the influence of modafinil. In particular, since fMRI possesses a good spatial resolution but lacks good temporal resolution, the applicability of a well-calibrated model promises to be instrumental in providing deeper insight into the influence of modafinil at time scales of milliseconds. In addition, the possibility of understanding the effect of modafinil on

different cortical and subcortical brain structures might prove useful in elucidating treatments for disorders such as ADHD, schizophrenia, autism, among others. Needless to say, a deeper understanding of modafinil mechanisms in the human brain is instrumental in order to clarify the issue of its positive or negative effects. As a final note, it should be pointed out that biologically plausible models not only offer the possibility of incorporating findings from different brain technologies, but also the opportunity to test mechanisms that could be experimentally unfeasible.

References

Ballon JS, Feifel D (2006) A systematic review of modafinil: potential clinical uses and mechanisms of action. J Clin Psychiatry 67:554–566

Bollimunta A (2011) Neuronal mechanisms and attentional modulation of corticothalamic alpha oscillations. J Neurosci 31(13):4935–4943

Bouret S, Sara SJ (2005) Network reset: a simplified overarching theory of locus coeruleus noradrenaline function. Trends Neurosci 28(11):574–582

Bransfield RC (2004) Potential uses of modafinil in psychiatric disorders. J Appl Res 4(2):198–207

Destexhe A (2000) Modeling corticothalamic feedback and gating of the thalamus by the cerebral cortex. J Physiol Paris 94(5–6):391–410

Ferraro L, Antonelli T, O'Connor WT, Tanganelli S, Rambert F, Fuxe K (1997) The antinarcoleptic drug modafinil increases gluatamate release in thalamic areas and hippocampus. Neuroreport 8(13):2883–2887

Franke AG, Lieb K (2010) Pharmacological neuroenhancement and brain doping: chances and risks. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 53(8):853–859

Frye MA, Grunze H, Suppes T, McElroy SL, Keck PE Jr, Walden J, Leverich GS, Altshuler LL, Nakelsky S, Hwang S, Mintz J, Post RM (2007) A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am J Psychiatry 164(8):1242–1249

Gallopin T, Luppi PH, Rambert FA, Frydman A, Fort P (2004) Effect of the wake-promoting agent modafinil on sleep-promoting neurons from the ventrolateral preoptic nucleus: an in vitro pharmacologic study. Sleep 27(1):19–25

Henderson DC, Louie PM, Koul P, Namey L, Daley TB, Nguyen DD (2005) Modafinil-associated weight loss in a clozapine-treated schizoaffective disorder patient. Ann Clin Psychiatry 17(2):95–97

Joos L, Docx L, Schmaal L, Sabbe BG, Dom G (2010) Modafinil in psychiatric disorders: the promising state reconsidered. Tijdschr Psychiatr 52(11):763–773

Keen D, Hadijikoumi I (2011) ADHD in children and adolescents. Clin Evid (Online) Feb 4, pii: 0312. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3217800/

Knie B, Mitra MT, Logishetty K, Chauhuri KR (2011) Excessive daytime sleepiness in patients with Parkinson's disease. CNS Drugs 25(3):203–212

Ledoux J, Farb R, Romanski L (1991) Overlapping projections to the amygdala and stiatum from auditory processing areas of the thalamus and cortex. Neurosci Lett 134:139–144

Minzenberg MJ, Watrous AJ, Yoon JH, Ursu S, Carter CS (2008) Modafinil shifts human locus coeruleus to low-tonic, high-phasic activity during functional MRI. Science 322(5908):1700–1702

Morrow GR, Shelke AR, Roscoe JA, Hickok JT, Mustian K (2005) Management of cancer-related fatigue. Cancer Invest 23(3):229–239

Nicholas R, Chataway J (2007) Multiple sclerosis. Clin Evid (Online), Aug 15, doi:pii: 1202. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2907805/

Scamell TE, Estabrooke IV, McCarthy MT, Chemelli RM, Yanagisawa M, Miller MS, Spacer CB (2000) Hypothalamic arousal regions are activated during modafinil-induced wakefulness. J Neurosci 20(22):8620–8628

Sugarman DE, Poling J, Sofuoglu M (2011) The safety of modafinil in combination with oral Δ9-tetrahydrocannabinol in humans. Pharmacol Biochem Behav 98(1):94–100

Téllez N, Montalbán X (2004) Modafinil and fatigue in multiple sclerosis. Neurologia 19(8):434–437

Trenado C, Haab L, Strauss DJ (2009) Corticothalamic feedback dynamics for neural correlates of attention. IEEE Trans Neural Syst Rehabil Eng 17(1):46–52

van Vliet SA, Vanwersch RA, Jongsma MJ, van der Gugten J, Olivier B, Philippens IH (2006) Neuroprotective effects of modafinil in a marmoset Parkinson model: behavioral and neurochemical aspects. Behav Pharmacol 17(5–6):453–462