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REVIEW

Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: A systematic review

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Abstract
Modafinil is an FDA-approved eugeroic that directly increases cortical catecholamine levels, indirectly upregulates cerebral serotonin, glutamate, orexin, and histamine levels, and indirectly decreases cerebral gamma-amino-butrytic acid levels. In addition to its approved use treating excessive somnolence, modafinil is thought to be used widely off-prescription for cognitive enhancement. However, despite this popularity, there has been little consensus on the extent and nature of the cognitive effects of modafinil in healthy, non-sleep-deprived humans. This problem is compounded by methodological discrepancies within the literature, and reliance on psychometric tests designed to detect cognitive effects in ill rather than healthy populations. In order to provide an up-to-date systematic evaluation that addresses these concerns, we searched MEDLINE with the terms "modafinil" and "cognitive", and reviewed all resultant primary studies in English from January 1990 until December 2014 investigating the cognitive actions of modafinil in healthy non-sleep-deprived humans. We found that whilst most studies employing basic testing paradigms show that modafinil intake enhances executive function, only half show improvements in attention and learning and memory, and a few even report impairments in divergent creative thinking. In contrast, when more complex assessments are used, modafinil appears to consistently engender enhancement of attention, executive functions, and learning. Importantly, we did not observe any preponderances for side effects or mood changes. Finally, in light of the methodological discrepancies encountered within this literature, we conclude with a series of recommendations on how to optimally detect valid, robust, and consistent effects in healthy populations that should aid future assessment of neuroenhancement.

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1. Introduction

"Neuroenhancement" refers to the targeted enhancement and extension of cognitive and affective abilities based on an understanding of their underlying neurobiology, and is increasingly represented by the media as an eventuality, usually in a desirable context. In reality, most contemporary strategies for neuroenhancement – comprising invasive and non-invasive brain stimulation and pharmacological manipulation – remain in their infancy. However, one agent, the FDA-approved eugeroic modafinil, has been extensively evaluated for cognitive modulation in healthy humans, and appears safe for widespread use. Unfortunately, discrepancies in methodology and outcomes within the literature have precluded consensus on the nature and degree of modafinil's effects on cognition, and continue to undermine discussions on the suitability of its off-label use as a cognitive enhancer, which is already thought to be extensive (Franke et al., 2013; Maher, 2008). In particular, studies using simple psychometric assessments derived from assessments of animal cognition or clinical populations have tended to report variable outcomes following modafinil intake (see, for example, Randall et al. (2003, 2004, 2005a, 2005b)), whereas more recent studies using complex testing paradigms have tended to report beneficial effects (see, for example, Finke et al. (2010)). Thus, we aim to provide an evaluation of modafinil as a neuroenhancement agent that addresses these discrepancies. To do so, we first introduce modafinil's molecular actions in the context of its pharmacological contemporaries, as well as the basic psychometric tests commonly employed to detect any alteration of cognition by these agents, before reporting the results of a systematic review on the cognitive effects of modafinil. We then follow this with methodological criticism of study designs employed to date, and offer a set of criteria that builds these observations into guidance for future study of neuroenhancement.

1.1. Modafinil and other pharmacological neuroenhancement agents

Pharmacological neuroenhancement agents may target online cognitive processes, such as attention and executive function, offline processes, such as memory consolidation, or a combination of the two. The stimulant methylphenidate (Ritalin©), which increases central catecholamine levels, appears to mainly target *online* processes, with some studies observing improvements in working memory, speed of processing, verbal learning and memory, and various attentional functions including vigilance (see Linssen et al. (2014); but see Repantis et al. (2010)). Despite the extensive attention that methylphenidate has received for cognitive enhancement, the significant side effect profile and high abuse potential that accompanies its use have curtailed discussions about wider societal use (Linssen et al., 2014). Conversely, piracetam, a racetam drug that may ameliorate cognitive decline in clinical populations (Waegemans et al., 2002), appears to target *offline* properties via modulation of acetylcholinergic and glutamatergic systems and increases in membrane permeability (Winblad, 2006), but appears to have limited effects in healthy humans (Dimond and Brouwers, 1976; Mindus et al., 1976). In addition, several herbal substances – namely *Panax ginseng*, *Ginkgo biloba*, and *Bacopa monneri*, all of which contain a mixture of neuroactive compounds attributed with pleiotropic molecular and cognitive effects – have been investigated for their potentiation of both online and offline processes (Aguiar and Borowski, 2013; Farooqui, 2012; Lü et al., 2009; Neale et al., 2013). However, methodological and evidential inconsistency within this *corpus* of research has obviated the demonstration of any robust effects on cognition.

Modafinil shares features with all of these agents: it is a stimulant drug, like methylphenidate; and, like the herbal substances and piracetam, exerts a complex neurochemical profile affecting both online and offline processes. Modafinil was first marketed in France in the 1990s as a eugeroic treatment for narcolepsy, and has since been FDA-approved for the treatment of excessive somnolence in narcolepsy, obstructive sleep apnoea, and shift work sleep disorder (Kumar, 2008). Modafinil directly inhibits central dopamine and noradrenaline uptake transporters, causing an elevation in catecholamine levels (Qu et al., 2008); these effects in turn elevate extracellular concentrations of serotonin, glutamate, histamine, and orexin, and reduce concentrations of gamma-amino-butrytic acid. Arousal- and wakefulness-promoting actions are thought to arise from these increases in dopaminergic and adrenergic transmission, and interactions with the orexin/hypocretin axis (Minzenberg and Carter, 2008). Although modafinil effects are thought to arise primarily from alterations in cortical neurotransmitter systems, similar neurochemical modulations have been reported in the hippocampus, thalamus, hypothalamus, amygdala, caudate, and midbrain (see Scoriels et al. (2013)).

1.2. Imaging studies

Modafinil does not appear to diffusely increase cortical activation (Ellis et al., 1999); rather, selective brain networks and inter-areal functional connectivity are altered. Resting-state imaging studies have shown that modafinil intake increases regional blood flow in bilateral precentral gyri, left hippocampus, left fusiform gyrus, bilateral lingual gyri, and cerebellum in narcoleptic and healthy participants (Joo et al., 2008). When Esposito and colleagues examined the activity of seven resting-state cortical networks, they found that in the absence of structural changes modafinil intake increases activity in the Dorsal Attention Network – thought to modulate externally-directed attention by amplifying or attenuating the saliency of relevant and irrelevant cues – and increased connectivity in the anterior cingulate cortex (ACC) node of the left Frontal Parietal Control network (Esposito et al., 2013) – which may mediate planning across domains (Spreng et al., 2010). On further analysis, this group found that although overall activity in the Saliency Network – which orients attention towards key environmental stimuli and helps guide behaviour – was unchanged, functional coupling between the right posterior insula, a key network node, and the rest of the network was strengthened (Cera et al., 2014).

1.3. Psychometric assessment of neuroenhancement

Research groups typically rely on two types of psychometric tests to assess altered neuropsychiatric states and provide