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Invited review

# Modafinil effects on cognition and emotion in schizophrenia and its neurochemical modulation in the brain

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ABSTRACT

Modafinil is a central nervous system wake promoting agent used for the treatment of excessive daytime sleeping. Its vigilance promoting properties and low abuse potential has intrigued the scientific community and has led to use it as a cognitive enhancer, before its neural functions were understood. Here, we review the effects of modafinil in human cognition and emotion and its specific actions on symptoms in patients with schizophrenia and whether these are consistently effective throughout the literature. We also performed a systematic review on the effects of modafinil on neurotransmitter signalling in different areas of the brain in order to better understand the neuromechanisms of its cognitive and emotional enhancing properties. A review of its effects in schizophrenia suggests that modafinil facilitates cognitive functions, with pro-mnemonic effects and problem solving improvements. Emotional processing also appears to be enhanced by the drug, although to date there are only a limited number of studies. The systematic review on the neurochemical modulation of the modafinil suggests that its mnemonic enhancing properties might be the result of glutamatergic and dopaminergic increased neuronal activation in the hippocampus and in the prefrontal cortex respectively. Other neurotransmitters were also activated by modafinil in various limbic brain areas, suggesting that the drug acts on these brain regions to influence emotional responses. These reviews seek to delineate the neuronal mechanisms by which modafinil affects cognitive and emotional function.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.



Modafinil (2-[(diphenylmethyl)sulphinyl]acetamide; Fig. 1) is a central nervous system wake promoting agent with low abuse potential used for the treatment of excessive daytime sleepiness.

Modafinil was created in the late 1970s and it was proposed as an experimental treatment for narcolepsy, due to its vigilance promoting actions (Goldenberg, 1986), although other behavioural effects and mechanisms of action were largely unknown. Research over the past forty years has led to the discovery that modafinil exerts wake promoting, concentration enhancing and mnemonic effects. However, there is still limited knowledge about its neuronal mechanisms of action.

## 1. Introduction on the effects of modafinil in cognitive and emotional functions

### 1.1. Effects of modafinil on cognitive function

#### 1.1.1. Sleeping disorders and healthy individuals

There is a large literature on narcolepsy and sleep deprived patients that has shown modafinil to enhance vigilance and attention (Gill et al., 2006; Hart et al., 2006; Wesensten et al., 2002), as one would expect, but also short-term memory (Pigeau et al., 1995), verbal flexibility (Walsh et al., 2004) and executive functions, which are cognitive control systems that manage other cognitive processes (Schwartz et al., 2004; Wesensten et al., 2005). Work on healthy individuals has shown that modafinil also enhanced executive function, including working memory, and inhibition control (i.e. being able to stop a response) (Muller et al., 2004; Randall et al., 2005; Turner et al., 2003; Sudgen et al., 2012).

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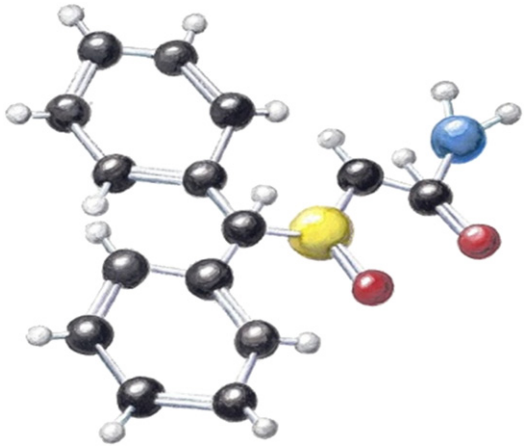

**Fig. 1.** Modafinil molecule structure. Drawing kindly provided by Bruno Scoriels.

*1.1.2. Attention deficit hyperactivity disorder (ADHD)*

Interest has grown in the potential beneficial cognitive effects of modafinil in mental disorders. Modafinil has been tested on patients with ADHD, with the hypothesis that the concentration enhancing properties of the drug might help attention deficits and hyperactivity. Several studies have shown that modafinil significantly enhanced attention functions in children with ADHD (Greenhill et al., 2006; Rugino and Copley, 2001; Rugino and Samsock, 2003; Biederman and Pliszka, 2008). Our group has shown that the drug enhanced short- and long-term memory, executive function and inhibition control in adults with ADHD (Turner et al., 2004a). Modafinil may therefore be a viable treatment for patients with ADHD; however, further chronic administration studies in patients with ADHD of the safety and efficacy of modafinil are needed.

*1.1.3. Schizophrenia and psychosis*

Modafinil has also been investigated as a potential candidate for treatment of cognitive deficits in schizophrenia (Morein-Zamir et al., 2007); our group has discovered that modafinil improves short- and long-term memory and cognitive flexibility in patients with chronic schizophrenia (Turner et al., 2004b). Other studies have shown that modafinil improves working memory (Rosenthal and Bryant, 2004), attention (Park et al., 2007), and inhibition control (Minzenberg et al., 2009) in schizophrenia. However, some studies have failed to find the expected cognitive enhancing properties in schizophrenia (Hunter et al., 2006; Pierre et al., 2007; Sevy et al., 2005; Spence et al., 2005), although no case of worsening of symptoms or cognitive functions have been observed in any of these studies.

Recent work has focused on first-episode psychosis, a time when deficits may be more tractable than in chronic schizophrenia, and where longer duration of untreated psychosis leads to greater severity of symptoms (Barnes et al., 2008; Marshall et al., 2005). Results indicate that modafinil enhances verbal and spatial working memory and improves accuracy in tasks measuring impulsivity (Scoriels et al., 2012). Modafinil had, however, no effect on sustained attention, attentional set-shifting, learning or fluency. The selective action of modafinil on working memory in first episode psychosis patients might have downstream effects on the key areas of social and occupational functioning.

*1.2. Effects of modafinil on emotional function*

*1.2.1. Narcolepsy and other sleeping disorders*

Modafinil's wake-promoting effects do not appear to be beneficial only for cognition, but also for emotional function. Several studies on sleep-deprived individuals have shown that modafinil is associated with enhanced levels of mood (Pigeau et al., 1995), sense of humour (Killgore et al., 2006) and confidence (Caldwell et al., 2004). Modafinil has been shown to reverse mood disruption in individuals working on night-shifts (Hart et al., 2006) and improve the quality of life in patients suffering from shift work sleep disorder (Erman et al., 2007). Quality of life has also been improved in patients suffering from narcolepsy after treatment with modafinil, particularly in the domains of vitality and social functioning (Becker et al., 2004).

The effects of modafinil on emotional functions other than mood and affective symptoms have been evaluated only in one study in the context of sleep deprivation in healthy volunteers. Huck and colleagues have tested the ability to discriminate and label simple emotional expressions versus complex affect blends, which have been created by morphing photographs of two different affective facial expressions. For simple affective faces, neither sleep loss nor modafinil made any difference to the accuracy of judgements. In contrast, for complex emotion blends, modafinil significantly improved the ability to discriminate subtle aspects of emotion correctly relative to placebo. These findings suggest that modafinil is effective at restoring some aspects of subtle affective perception (Huck et al., 2008).

*1.2.2. Healthy individuals, depression and bipolar disorders*

Results are mixed with regards to the anxiogenic and anxiolytic effects of modafinil in the healthy versus mentally ill population. On one hand, Randall and colleagues have found that healthy individuals taking 100 mg of modafinil exhibited increased somatic anxiety symptoms compared to placebo or 200 mg modafinil (Randall et al., 2003). Taneja and colleagues have found a similar anxiogenic effect for modafinil administered at 400 mg daily; however, increased general mood and a significant effect on positive affect scales have also been observed (Taneja et al., 2007). Moreover, modafinil has been shown to improve symptoms of anxiety and depression in depressed (Price and Taylor, 2005) and bipolar patients (Frye et al., 2007).

*1.2.3. Schizophrenia and psychosis*

There are no published studies that have evaluated the effects of modafinil on affect recognition, changes of mood or other emotional functions in chronic schizophrenia. Our group has tested for the first time emotional impairments in patients with a first episode of psychosis, with tests assessing emotional face recognition, affective impulsivity, reward and punishment learning, and subjective mood changes (Scoriels et al., 2011). Modafinil improved the recognition of facial expressions for all categories of emotions and significantly so for sad faces. There were no significant effects of modafinil on subjective assessments of mood, indicating that improvements in emotional face recognition are specific to the emotional component. The improvement by modafinil of emotional discrimination may improve individual adaptation to particular emotional situations and consequent elevation of mood. Good face processing skills can promote social competence (Hooker and Park, 2002; Ihnen et al., 1998; Mueser et al., 1996) and predict later work performance and independent living in schizophrenia patients (Kee et al., 2003). In contrast, modafinil did not show any significant effects on tasks measuring emotional sensitivity to reward or punishment, or interference of emotional valence on cognitive function.

To further our knowledge on the mechanisms of action of modafinil, we performed two systematic reviews. The first review assessed the effects of modafinil in people with schizophrenia disorders and first episode psychosis, with a particular focus on its effects in cognitive and emotional functions. The second review

targeted the modulatory effects of modafinil on neurotransmission systems in specific regions of the brain. The latter aimed to understand the biological mechanisms by which modafinil exerts its cognitive and emotional enhancing properties.

## 2. Systematic review of modafinil in schizophrenia

### 2.1. Individual studies included in the review

In order to better understand the effects of modafinil in schizophrenia, we searched the peer-reviewed literature in PubMed, SCOPUS, and EMBASE for all studies that have used modafinil in randomized, single or chronic dosage, placebo-controlled, parallel or crossover designs in patients with schizophrenia or first episode psychosis. Different combinations of the terms 'modafinil' and 'schizophrenia' and 'psychosis' were used. Studies were excluded for the following reasons: pilot studies, studies not randomized or placebo controlled, studies using a different compound than modafinil (e.g. armodafinil), or overlap of reported data between papers. Nine studies fulfilling these criteria were identified by April 2012 (Table 1). There were five single dose administration crossover designed studies (Farrow et al., 2006; Minzenberg et al., 2008; Scoriels et al., 2012; Spence et al., 2005; Turner et al., 2004b) and four chronic dose administration (8 weeks) parallel designed studies (Arbabi et al., 2012; Freudenreich et al., 2009; Pierre et al., 2007; Sevy et al., 2005). In total, these studies involved 228 patients, with various diagnoses (first episode psychosis, schizophrenia, schizoaffective disorders), different age ranges (range: 25–49.8, average: 38.3 years of age), sex-ratios (range: 0.4–9.5, average: 3.3), IQ scores (these were not systematically collected), duration of illness (range: 1.4–19.5, average: 12.2 years) and anti-psychotic prescription (six studies included patients on several antipsychotics and two studies examined the specific interaction between modafinil and clozapine and risperidone, respectively). These nine studies also administered different doses of modafinil (range: 100–300, average: 178) (Table 1).

### 2.2. Summary results

Outcome measures included psychiatric symptoms, cognition, emotion, global functioning, motor functioning, fatigue, and drug effect. Side effects were also accounted for. Psychotic symptoms were assessed for overall symptoms, positive and negative symptoms and depression symptoms. Cognition was assessed in the domains of memory, learning, attention, fluency, control, flexibility, problem solving, and face recognition. Emotion was assessed in the domains of facial emotion recognition, emotional control, and subjective mood. Results from the nine studies (Table 2) have been qualitatively analysed because the diversity of the tests used did not allow a meta-analysis to be performed.

Table 2 shows that 12 outcome measures improved with modafinil administration, 71 showed no statistically significant differences between modafinil and placebo administration, and none was impaired by the drug.

Assessment of psychiatric symptoms was performed in chronic modafinil administration studies. The studies carried out by Pierre et al. (2007) and Arbabi et al. (2012) showed improvement in three clinical global impression symptoms scales. However, the remaining 12 measures on psychiatric symptoms did not show any difference with drug administration; neither did the three measures of global functioning, nor the five measures of fatigue. Farrow and colleagues showed that acute administration of modafinil enhanced unconstrained motor activity (Farrow et al., 2006). This has not been replicated in studies with acute or chronic dosage designs. However, these studies were based on questionnaires that reported subjective perception of motoric activity, unlike Farrow's study that measured the effect of modafinil in actual motor activity in patients.

As for cognition, results were more promising. Working memory showed improvements with modafinil in two single dose crossover designed studies (Scoriels et al., 2012; Turner et al., 2004b). The same studies also showed isolated positive results in cognitive control (Scoriels et al., 2012) and flexibility (Turner et al., 2004b). However, other studies that assessed the same cognitive domains generally failed to confirm improvement. Two independent studies showed that modafinil induced an increase in latency related to problem solving (Scoriels et al., 2012; Turner et al., 2004b).

The effect of modafinil on emotional functioning in schizophrenia has only recently been investigated. Emotional outcome measures showed an improvement in emotional face recognition with modafinil, which appeared to be independent of potential improvements in non-emotional face recognition (Scoriels et al., 2011). However, this is the only study that has assessed emotional functions in the context of schizophrenia and related disorders. These effects of the drug in emotional functions definitely warrant further exploration.

### 2.3. Interpretation

The systematic review and synthesis of randomised double-blind, placebo-controlled studies using modafinil for the treatment of schizophrenia and related disorders suggests that the drug has beneficial effects in patients' cognitive, emotional, functional and motor dysfunctions.

Working memory appeared to be specifically improved with modafinil administration. In fact, the drug enhanced digit and spatial working memory in two independent studies that assessed

**Table 1**
Randomised trials of modafinil in schizophrenia or related condition.

| Authors | Diagnostic | Age | Sex ratio | IQ | Illness duration (years) | Subjects on anti-psychotic drugs | Sample size | Study design | Dosage (mg) |
|---|---|---|---|---|---|---|---|---|---|
| Scoriels et al. (2011) | FEP | 25 | 3.6 | 112 | 1.4 | yes | 40 | CS | 200 |
| Minzenberg et al. (2008) | SZ | 33 | 1.3 | ? | 19.5 | yes (atypical) | 20 | CS | 200 |
| Turner et al. (2004b) | SZ | 43 | 4 | 110 | 17.3 | yes (atypical) | 20 | CS | 200 |
| Farrow et al. (2006) | SZ | 38 | males | ? | 15 | yes | 18 | CS | 100 |
| Spence et al. (2005) | SZ | 38 | males | >70 | ? | ? | 17 | CS | 100 |
| Freudenreich et al. (2009) | SZ or SZA | 45 | 3.4 | 97 | ? | Clozapine | 35 | PC | 250 |
| Arbabi et al. (2012) | SZ | 34 | 3.2 | ? | 7.5 | Risperidone | 46 | PC | 200 |
| Pierre et al. (2007) | SZ or SZA | 50 | 9.5 | ? | ? | yes | 20 | PC | 180 |
| Sevy et al. (2005) | SZ SZA | 37 | 0.4 | ? | 12.5 | yes (atypical) | 20 | PC | 175 |

CS = Crossover design, Single dosage; FEP = first episode psychosis; PC = Parallel design, Chronic dosage (8 weeks); SZ = schizophrenia; SZA = schizophrenia affective disorder; ? = Not stated.

**Table 2**
Outcome measures from modafinil administration studies in schizophrenia or related disorders.

| | Scoriels et al. (2011) | Minzenberg et al. (2008) | Turner et al. (2004b) | Farrow et al. (2006) | Spence et al. (2005) | Freudenreich et al. (2009) | Arbabi et al. (2012) | Pierre et al. (2007) | Sevy et al. (2005) |
|---|---|---|---|---|---|---|---|---|---|
| **Cognition** | | | | | | | | | |
| Working memory | 1↑ | – | 1↑ | – | 1Ø | 1Ø | – | – | 2Ø |
| Spatial working memory | 1↑ | – | 2Ø | – | – | – | – | – | – |
| Memory (other) | – | – | 2Ø | – | – | – | – | – | 2Ø |
| Problem solving | 1↑ | – | 1↑ | – | – | – | – | – | – |
| Control | 1↑ | 1Ø | 1Ø | – | 1Ø | – | – | – | – |
| Flexibility | 1Ø | – | 1↑ | – | – | 2Ø | – | 1Ø | – |
| Learning | 2Ø | – | – | – | – | 1Ø | – | 1Ø | 2Ø |
| Attention | 1Ø | – | – | – | – | 1Ø | – | 1Ø | 1Ø |
| Fluency | 1Ø | – | – | – | – | 1Ø | – | – | – |
| Face recognition | 1Ø | – | – | – | – | 1Ø | – | – | – |
| **Emotion** | | | | | | | | | |
| Emotional face recognition | 1↑ | – | – | – | – | – | – | – | – |
| Emotional control | 1Ø | – | – | – | – | – | – | – | – |
| Subjective mood | 1Ø | – | 1Ø | – | – | – | – | – | – |
| **Psychiatric symptoms** | | | | | | | | | |
| Overall symptoms | – | – | – | – | – | 2Ø | 1↑ | 1↑, 2Ø | 3Ø |
| Positive and negative | – | – | – | – | – | 2Ø | 1↑ | 1Ø | 1Ø |
| Depression | – | – | – | – | – | – | – | – | 1Ø |
| **Other measures** | | | | | | | | | |
| Global functioning | – | – | – | – | – | 2Ø | – | 1Ø | – |
| Motor functioning | – | – | – | 1↑ | 2Ø | 1Ø | – | – | 2Ø |
| Fatigue | – | – | – | – | – | 2Ø | – | – | 3Ø |
| Drug effect | – | – | – | – | – | – | – | – | 1Ø |

1, 2, or 3 = Number of outcome measures assessed in the study.
– = Outcome measure not assessed in the study.
↑ = Outcome measure that showed a statistically significant improvement with modafinil administration.
Ø = Outcome measure that did not show statistically significant differences between placebo and modafinil administration.

different patient populations with different age ranges, diagnoses, and duration of illness (Scoriels et al., 2012; Turner et al., 2004b), suggesting that this cognitive function is highly sensitive to the drug, independent of these potentially confounding factors. The increased latency with modafinil in two problem-solving tasks from the same independent studies was also of interest. It suggests patients allow themselves more time to solve problems (i.e. preventing the tendency to 'jump to conclusions'), which resulted in a trend for accuracy improvement in one of the studies (Turner et al., 2004b). The jumping to conclusion bias has previously been linked with impairments in working memory and modafinil may ameliorate those, hence improving delusional ideation (Broome et al., 2007). There were also isolated results of improvement in the cognitive control (Scoriels et al., 2012) and flexibility (Turner et al., 2004b) domains. However, these have not been replicated in the studies that have also assessed these cognitive functions (Freudenreich et al., 2009; Minzenberg et al., 2008; Pierre et al., 2007; Scoriels et al., 2012; Spence et al., 2005; Turner et al., 2004b). It may be that the modulation by modafinil of these specific domains, i.e. cognitive control and flexibility, might be more sensitive to demographic and study design factors, such as age, sex-ratio, IQ, duration of illness, medication, chronic versus single dosage designs or dose of modafinil administered. Indeed, the nine studies reported in this review show great differences in these factors. For example, none of the studies analysing the chronic effects of modafinil showed any effects in cognitive domains, whereas most of the single dose designed studies outcome measures did show an improvement with modafinil administration in these domains. This may suggest that modafinil should be taken acutely, whenever patients need it for specific challenging situations, rather than chronically, hence minimising unnecessary potential side effects, and getting the most efficient action of the drug. There is also the possibility that modafinil may create tolerance effects when taken chronically. Volkow and colleagues showed that modafinil activated brain areas that contribute to addictive behaviour, such as the caudate, putamen, and nucleus accumbens (Volkow et al., 2009). Other factors, such as level of performance at baseline may also contribute to differential effects of the drug. Indeed, the two studies showing the most proficient effects of modafinil in cognitive functions assessed participants with quite high IQs (Scoriels et al., 2012; Turner et al., 2004b). Not all the studies reported IQ measures, but the ones that did, tested participants with significantly lower IQs (Freudenreich et al., 2009; Sevy et al., 2005). Thus, it may be hypothesised that the cognitive enhancing properties of modafinil are most efficacious when the baseline level of performance is relatively high, which confirms modafinil's efficacy in healthy controls. And finally, it is important to take into consideration the interaction that antipsychotic medication may have on the effects of modafinil. Two studies examined the effect of modafinil in combination with specific antipsychotics, i.e. risperidone and clozapine, respectively (Arbabi et al., 2012; Freudenreich et al., 2009). The study with risperidone did not report the assessment of any cognitive function, but was efficient in the improvement of positive and negative symptoms in patients tested with risperidone and modafinil, more than those tested with risperidone on its own. The study with clozapine and modafinil assessed several cognitive domains, as well as psychiatric symptoms, global and motor functioning and fatigue. Surprisingly, and despite a good design and demographics that appear to be reflective of the general population with schizophrenia, modafinil showed no statistically significant improvement in any of the domains tested. Clozapine is perhaps the most efficacious antipsychotic medication but due to the risk of potentially fatal blood dyscrasias, its use is largely confined to those in whom other antipsychotics have failed (Lewis et al., 2006). It is an antagonist at dopaminergic, serotonergic, cholinergic, as well as histamine and adrenergic receptors (Humbert-Claude et al., 2012; Philibin et al., 2009). The drug has complex effects at GABA and

**Table 3**
Modafinil action, by brain region and neurotransmitter system.

| Brain regions | Neuronal activity | Glutamate system | GABAergic system | Dopamine system | Noradrenaline system | Serotonergic system | Histamine system | Orexin system |
|---|---|---|---|---|---|---|---|---|
| **CORTEX** | | | | | | | | |
| **prefrontal cortex** | ↑ (100mg, schizophrenics) control task (Hunter, 2006)<br>↑ (200mg, human) control task (Minzenberg, 2008)<br>↑ (208mg, narcoleptics) (Joo, 2008)<br>↑↑ (10mg/kg, rat) (Gozzi, 2012)<br>↓ (100mg, human) working memory task (Rasetti, 2010)<br>↓ (200mg, human) reaction time task (Minzenberg, 2011) | ↑ NMDA R (64mg/kg, rat) attention shifting task with PCP block (Dawson, 2010)<br>ø NMDA R (125 mg/kg, mouse) (Nguyen, 2011) | ø GABA A R (125 mg/kg, mouse) (Nguyen, 2011) | ↑ (128 mg/kg, rat) (Saint Hilaire, 2001)<br>↑ DAT (125 mg/kg, mouse) (Nguyen, 2011) | ↑ (128 mg/kg, rat) (Saint Hilaire, 2001) | ↑ (128 mg/kg, rat) (Saint Hilaire, 2001)<br>ø (3 mg/kg) & ↑ (3 mg/kg + fluoxetine and imipramine, rat) (Ferraro, 2005) | | |
| **forebrain** | | | | NA transporter blocked + D2/3 autoR activation : modafinil effect blunted mice (Wisor, 2005) | NA transporter blocked + Adrenergic alpha 1 R blocked : modafinil effect blunted (90mg/kg, mouse (Wisor, 2005)<br>NA transporter blocked : ø on modafinil awakening (90mg/kg, mouse) (Wisor., 2005) | | | |
| **frontal cortex** | ↑ (150mg/kg, rat) (Scammell, 2000)<br>↑ (64mg/kg, mouse) (Pierard, 2007)<br>ø (300mg/kg, rat) (Engber, 1998) | | | | | ↑ (10, 30,100 mg/kg in vivo rat) (Ferraro, 2002) | | |
| **fronto-parietal cortex** | | ø (64mg/kg) & ↑ (128mg/kg, rat) (Touret, 1994) | | | | | | |
| **parietal cortex** | ↑ (200mg, human) reversal learning task (Ghahremani, 2011)<br>↓ (200mg, human) reaction time task (Minzenberg, 2011) | ↓ (200mg, human) reaction time task (Minzenberg, 2011) | ↓ (30 mg/kg, guinea pig) (Tanganelli, 1994) | | | | | |
| **temporal cortex** | ↑ (1, 2.5, 5mg/kg cat & rat) (Lin, 1996) | | | | | | | |
| **occipito-temporal cortex** | ↑ (200mg, human) reversal learning task (Ghahremani, 2011)<br>↓ (208mg, narcoleptics) (Joo, 2008) | | | | | | | |

**Table 3.** (*continued*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **occipital cortex** | ↓ (208mg, narcoleptics) (Joo, 2008) | | | | | | | |
| **cerebral cortex** | ↑ (1, 2.5, 5mg/kg cat) (Lin, 1996)<br>↑ (in vitro, mice) (Urbano, 2007) | ↑ mRNA (128 mg/kg, rat) (Touret, 1994) | ↓ (3-30mg/kg, guinea pig) (Tanganelli, 1992)<br>↓ (30-100mg/kg rat) (Ferraro, 1997)<br>↓ (150mg/kg, rat) (Scammell, 2000)<br>ø (0.3 & 1uM) & prevented ↓ in GABA release electrically induced with glutamate in vitro rat) (Antonelli, 1998) | | ↑ (30mg/kg, when serotonergic neurons killed, guinea pig) (Tanganelli, 1995) | ↑ (3-100 mg/kg in vivo and electrically-evoked with 0.3-30uM in vitro rat) (Ferraro, 2000)<br>ø (1-30 M, rat) (Ferraro, 2001) | | |
| **cingulate cortex** | ↑ (150mg/kg, rat) (Scammell, 2000)<br>↑↑ (10mg/kg, rat) (Gozzi, 2012)<br>↑ (300mg, rat) (Engber, 1998)<br>↓ (100mg, human) on executive task (Rasetti, 2010)<br>↓ (200mg, human) reaction time task (Minzenberg, 2011) | ↑ NMDA R (64mg/kg, rat) attention shifting task with PCP block (Dawson, 2010)<br>ø NMDA R (125 mg/kg, mouse) (Nguyen, 2011) | ø GABA A R (125 mg/kg, mouse) (Nguyen, 2011) | | | | | |
| **pyriform cortex** | ↑ (150mg/kg, rat) (Scammell, 2000) | | | | | | | |

| Brain regions | Neuronal activity | Glutamate system | GABAergic system | Dopamine system | Noradrenaline system | Serotonergic system | Histamine system | Orexin system |
|---|---|---|---|---|---|---|---|---|
| **HIPPOCAMPUS** | | | | | | | | |
| **hipocampus** | ↑ (300mg, rat) (Engber, 1998)<br>↑ (64mg/kg, mouse) (Pierard, 2007)<br>↑ (100-400mg, narcoleptic & normal humans) (Kim, 2007)<br>↑ (200mg/kg, rat) (He, 2011)<br>↑ (64mg/kg, rat) (Tsanov, 2010)<br>↑ (10mg/kg, rat) Gozzi, 2012)<br>↓ (208mg, narcoleptics) (Joo, 2008) | ø (30-60-100mg) & ↑ (300mg, rat) (Ferraro, 1997)<br>ø NMDA R (125 mg/kg, mouse) (Nguyen, 2011) | ø (30-60-100mg) & ↓ (300mg, rat) (Ferraro, 1997)<br>↓ (0.1, 1 mM, in vitro rat) (Huang et, 2008)<br>ø GABA A R (125 mg/kg, mouse) (Nguyen, 2011) | | | | | |

(*continued on next page*)

**Table 3.** (*continued*)

| Brain regions | Neuronal activity | Glutamate system | GABAergic system | Dopamine system | Noradrenaline system | Serotonergic system | Histamine system | Orexin system |
|---|---|---|---|---|---|---|---|---|
| **AMYGDALA** | | | | | | | | |
| **periamygdala + praepyriformis cortex** | ↑ (1, 2.5, 5mg/kg cat & rat) (Lin, 1996) | | | | | ↑ (10, 30,100 mg/kg in vivo rat) (Ferraro, 2002) | | |
| **central nucleus** | ↑ (75, 150, 300mg/kg, rat) (Scammell, 2000) | | | | | | | |
| | ø (10-1000nM, rat) (Silvestri, 2002) | | | | | | | |
| **amygdala** | ↑ (300mg/kg, rat) (Engber, 1998) | | | | | | | |
| | ↑ (64mg/kg, mouse) (Pierard, 2007) | | | | | | | |
| | ↓ (100mg, human) on emotional task (Rasetti, 2010) | | | | | | | |

| Brain regions | Neuronal activity | Glutamate system | GABAergic system | Dopamine system | Noradrenaline system | Serotonergic system | Histamine system | Orexin system |
|---|---|---|---|---|---|---|---|---|
| **HYPOTHALAMUS** | | | | | | | | |
| **medial hypothalamus** | | | | ø (128 mg/kg, rat) (Saint Hilaire, 2001) | ↑ (128 mg/kg, rat) (Saint Hilaire, 2001) | ↑ (128 mg/kg, rat) (Saint Hilaire, 2001) | | |
| **anterior hypothalamus** | ↑↑ (1, 2.5, 5mg/kg cat & rat) (Lin, 1996) | | | | | | ↑ (150 mg/kg, rat) (Ishizuka, 2003) | |
| | ↑ (300mg/kg, rat) (Engber, 1998) | | | | | | | |
| | ↑ (64mg/kg, mouse) (Pierard, 2007) | | | | | | | |
| | ↑ (10, 20, 30 g/kg, rat) (Murillo-Rodriguez, 2008) | | | | | | ↑ (150 mg/kg, rat) (Ishizuka, 2007) | |
| | ↑ (10, 20, 30 g/kg, rat) (Arias-Carrion, 2011) | | | | | | | |
| | ø (75, 150, 300mg/kg, rat) (Scammell, 2000) | | | | | | | |
| **posterior hypothalamus** | | ↑ (30-300 mg, rat) (Ferraro, 1999) | ø (30-60mg ) & ↓ (100 mg via 5HT3R, rat) (Ferraro, 1996/1997) | | | ↑ (100 mg/kg in vivo rat) (Ferraro, 2002) | | |
| | | | ↓ (30-300 mg, rat) (Ferraro, 1999) | | | | | |
| | | | ↓ (75, 150mg/kg, rat) (Scammell, 2000) | | | | | |
| | | | ↓ (cat) (Lin - unpublished) | | | | | |

**Table 3.** (*continued*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **lateral hypothalamus** | | | | | | | | ↑ (150 mg/kg, mouse) (Chemelli, 1999)<br>↑ via glutamate (10mg/kg, mouse) (Rao, 2007, 2009) |
| **paraventricular nucleus of hypothalamus** | ↑ (300mg/kg, rat) (Engber, 1998) | | | | | | | |
| **hypothalamus** | | ø on glutamate synthesis (100 mg/kg ex-vivo rat) (Perez de la Mora, 1999) | ø on GABA synthesis (100 mg/kg ex-vivo rat) (Perez de la Mora, 1999) | | | | ↑ (150 mg/kg, mouse with intact orexin neurons) (Ishizuka, 2010) | |
| **perifornical area** | | | | | | | | ↑ (75, 150mg/kg, rat) (Scamell, 2000) |
| **medial preoptic area** | | ↑ (30-300mg, rat) (Ferraro, 1999) | ø (30mg) & ↓ (60-100mg, rat) (counteracted by 5HT3R) (Ferraro, 1996/1997)<br>↓ (30-300mg, rat) (Ferraro, 1999) | | | ↑ (100 mg/kg in vivo rat) (Ferraro, 2002) | | |
| **Ventro lateral preoptic area** | ø (75, 150mg/kg), ↓ (300mg/kg, rat) (Scammell, 2000) | | | | ↑ (in vitro rat) (Gallopin, 2004) | | | |
| **suprachiasmatic nuclei** | ↑ (300mg/kg, rat) (Engber, 1998)<br>↑ (64mg/kg, mouse) (Pierard, 2007)<br>ø (75, 150, 300mg/kg, rat) (Scammell, 2000) | | | | | | | |
| **Tubero-mammilary nucleus** | ↑ (150 mg/kg, mouse with intact orexin neurons) (Ishizuka, 2010)<br>↑ (75, 150, 300mg/kg rat) (Scammell, 2000) | | | | | | ø (1nmol, rat) (Ishizuka, 2003) | |

| Brain regions | Neuronal activity | Glutamate system | GABAergic system | Dopamine system | Noradrenaline system | Serotonergic system | Histamine system | Orexin system |
|---|---|---|---|---|---|---|---|---|
| **THALAMUS** | | | | | | | | |
| **medial thalamus** | ↑ (10mg/kg, rat) (Gozzi, 2012) | | | | ↑ (5-8mg/kg, monkey) (Madras, 2006) | | | |
| **ventrolateral thalamus** | ↑ (300mg/kg, rat) (Engber, 1998) | ø (30mg) & ↑ (60-100-300mg, rat) (Ferraro, 1997) | ø (30-100mg) & ↓ (300mg, rat) (Ferraro, 1997) | | | | | |

(*continued on next page*)

**Table 3.** (*continued*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **ventromedial thalamus** | ø (300mg/kg, rat) (Engber, 1998) | ø (30mg) & ↑ ↑ (60-100-300mg, rat) (Ferraro, 1997) | ø (30-100mg) & ↓ (300mg, rat) (Ferraro, 1997) | | | | | |
| **thalamus** | ↑ (0.2 - 200 M, in vitro mice) (Urbano, 2007) | ø NMDA R (64mg/kg, rat) attention shifting task with PCP block (Dawson, 2010) | | | | | | |

| Brain regions | Neuronal activity | Glutamate system | GABAergic system | Dopamine system | Noradrenaline system | Serotonergic system | Histamine system | Orexin system |
|---|---|---|---|---|---|---|---|---|
| **BASAL GANGLIA** | | | | | | | | |
| **striatum** | ↑↑ (1, 2.5, 5mg/kg cat) (Lin, 1996) | ø (100mg, rat) (Ferraro, 1998) | ↓ (100 &300mg, rat) (Ferraro, 1998) | prevention of ↓ by MPTP but does not increase on its own, (10-100mg/kg, mouse) (Fuxe, 1992) | prevention of ↓ (50 & 100mg/kg, mice) (Xiao, 2004) | prevention of ↓s (50 & 100mg/kg, mice) (Xiao, 2004) | | |
| | | | | prevention of ↓, (100mg/kg, rat) (Ueki, 1993) | | | | |
| | ↑ (10mg/kg, rat) (Gozzi, 2012) | | ↓ (150mg/kg, rat) (Scamell, 2000) | prevention of ↓, (100mg/kg, mouse) (Aguirre, 1999) | | | | |
| | ↑ (150, 300mg/kg, rat) (Scammell, 2000) | ø on MPTP induced ↑ (50 & 100mg/kg, mice) (Xiao, 2004) | | prevention of ↓ (50 & 100mg/kg, mice) (Xiao, 2004) | | | | |
| | | | ↓ MPTP induced increase (50 & 100mg/kg, mice) (Xiao, 2004) | ↑ DAT (5-8mg/kg, monkey) (Madras, 2006) | | | | |
| | ø (300mg/kg, rat) (Engber, 1998) | | | ø in presynaptic DA neurons, (16-256mg/kg, mouse) (Sereville, 1994) | | | | |
| **caudate nucleus** | ↑↑ (1, 2.5, 5mg/kg cat & rat) (Lin, 1996) | ø NMDA R (125 mg/kg, mouse) (Nguyen, 2011) | ø GABA A R (125 mg/kg, mouse) (Nguyen, 2011) | ↑ (90mg/kg, dog) (Wisor, 2001) | | | | |
| | | | | ↑ (D2/3 R, DAT, 200, 400mg, human) (Volkow, 2009) | | | | |
| | | | | ↑ (10mg/kg, monkey) (Andresen, 2010) | | | | |
| | ↑ (150mg/kg, rat) (Scammell, 2000) | | | ↑ DAT, D1R (125 mg/kg, mouse) (Nguyen, 2011) | | | | |
| | | | | ↓ D2R (125 mg/kg, mouse) (Nguyen, 2011) | | | | |
| **putamen** | ↑ (150mg/kg, rat) (Scammell, 2000) | ø NMDA R (125 mg/kg, mouse) (Nguyen, 2011) | ø GABA A R (125 mg/kg, mouse) (Nguyen, 2011) | ↑ (D2/3 R, DAT, 200, 400mg, human) (Volkow, 2009) | | | | |
| | | | | ↑ DAT, D1R (125mg/kg, mouse) (Nguyen, 2011) | | | | |
| | | | | ↑ (10mg/kg, monkey) (Andresen, 2010) | | | | |
| | | | | ↓ D2R (125 mg/kg, mouse) (Nguyen, 2011) | | | | |
| **nucleus accumbens** | ↑ (300mg/kg, rat) (Engber, 1998) | ø NMDA R (125 mg/kg, mouse) (Nguyen, 2011) | ↓ (30-300mg/kg, rat) (Ferraro, 1996/1997) | ↑ DAT, D1R (125 mg/kg, mouse) (Nguyen, 2011) | | ø (20, 60mg/kg, rat) (Zolkowska, 2009) | | |
| | | | | ↑ (30-300mg/kg, rat) (Ferraro, 1997) | | | | |

**Table 3.** (*continued*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | ø (75, 150mg/kg, rat) (Scammell, 2000) | | | ↑ (10ug/5 l, rat) (Murillo-Rodriguez, 2007)<br>↑ (20, 60mg/kg DA, 10 M DAT, rat) (Zolkowska, 2009)<br>↑ (D2/3 R, DAT, 200, 400mg, human) (Volkow, 2009)<br>↓ D2R (125 mg/kg, mouse) (Nguyen, 2011)<br>↓ (10ug/5ul, rat) (Murillo-Rodriguez, 2007) | | | | |
| **globus pallidus** | | ø (100mg, rat) (Ferraro, 1998) | ↓ (100 &300mg, rat) (Ferraro, 1998)<br>ø (10, 30mg/kg +MPTP) & ↓ (100mg/kg + MPTP) on GABA receptor activation, marmoset (Zeng, 2004) | | | | | |
| **substantia nigra** | | prevention of ↓ (50 & 100mg/kg, mice) (Xiao, 2004)<br>ø (300 mg, rat) (Ferraro, 1998) | prevention of ↓ (50 & 100mg/kg, mice) (Xiao, 2004)<br>ø (20 M in vitro rat) (Korotkova, 2007)<br>ø (100mg) & ↓ (300mg, rat) (Ferraro, 1998) | prevention of ↓ by MPTP but does not increase on its own, (10-100mg/kg, mouse) (Fuxe, 1992)<br>prevention of ↓ by MPTP, (100mg/kg, rat) (Ueki, 1993)<br>prevention of ↓ MPTP induced (10, 30 & 100mg/kg, marmoset) (Jenner, 2000)<br>partial prevention of MPTP DA degeneration, (100mg/kg, marmoset) (Vliet, 2008)<br>↑ D1R (125 mg/kg, mouse) (Nguyen, 2011)<br>ø in firing neurons,(128mg/kg, rat) (Akaoka, 1991)<br>ø in presynaptic DA neurons, (16-256mg/kg, mouse) (Sereville et al., 1994)<br>↓ of firing (20 M in vitro rat) (abolished by sulpiride (D2 antagonist) (Korotkova, 2007) | ø (20 M + prazosine in vitro rat) (Korotkova, 2007) | | | |
| **ventral tegmental area** | ø (100, 300mg/kg, rat) (Engber, 1998)<br>ø (75, 150mg/kg, rat) (Scammell, | | ø (20 M in vitro rat) (Korotkova, 2007) | ø in firing neurons,(128mg/kg, rat) (Akaoka, 1991)<br>↓ of firing (20 M in vitro rat) (abolished | ø (20 M + prazosine (alpha1 adrenoR) in vitro rat) (Korotkova, 2007) | | | |

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**Table 3.** (*continued*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2000) | | | by sulpiride (D2 antagonist) (Korotkova, 2007) | | | | |

| Brain regions | Neuronal activity | Glutamate system | GABAergic system | Dopamine system | Noradrenaline system | Serotonergic system | Histamine system | Orexin system |
|---|---|---|---|---|---|---|---|---|
| **MIDBRAIN** | | | | | | | | |
| **locus coeruleus** | ↓ (rest) & ↑ (control task,200mg, human) (Minzenberg, 2008)<br>↑ (75, 150mg/kg, rat) (Scammell, 2000) | ø (64mg/kg) & ↑ (128mg/kg, rat) (Touret, 1994) | | | ø in firing neurons,(128mg/kg, rat) (Akaoka, 1991) | | | |
| **pontine reticular field** | ø (100, 300mg/kg, rat) (Engber, 1998) | | | | | | | |
| **pedunculopontine tegmental nucleus** | ↑ (10, 20, 30 g/kg, rat) (Murillo-Rodriguez, 2008; Arias-Carrion, 2011) | | | | | | | |
| **dorsal raphe** | ↑ (10mg/kg, rat) (Gozzi, 2012)<br>ø (75, 150mg/kg, rat) (Scammell, 2000) | | | | | ↑ (10, 30,100 mg/kg in vivo rat) (Ferraro, 2002)<br>ø (3 mg/kg) & ↑ (3 mg/kg + fluoxetine, rat) (Ferraro, 2005) | | |
| **olivary nucleus** | ↑ (0.2-200 M, in vitro mouse) (Urbano, 2007) | | | | | | | |

| | Neuronal activity | Glutamate system | GABAergic system | Dopamine system | Noradrenaline system | Serotonergic system | Histamine system | Orexin system |
|---|---|---|---|---|---|---|---|---|
| **SUMMARY** | | | | | | | | |
| **Overall brain regions** | ↑ in 50/71 brain regions studied (ø in 11/71 and ↓ in 10/71) | ø in 12/24 brain regions studied ( ↑ in 11/24 and ↓ in 1/24) | ↓ in 22/32 brain regions studied ( ø in 9/32 and↑ in 1/32) | ↑ in 25/36 brain regions studied (ø in 5/36 and ↓ in 6/36) | ↑ in 7/11 brain regions studied (ø in 4/11) | ↑ in 11/13 brain regions studied (ø in 2/13) | ↑ in 3/4brain regions studied (ø in 1/4) | ↑ in 3/3 brain regions studied |

ø — no change of activity or neurotransmitter release with modafinil administration

↑ or prevention of ↓ — increase of activity or neurotransmitter release with modafinil administration

↓ — decrease of activity or neurotransmitter release with modafinil administration

NMDA receptors, and there is evidence that its active metabolites may be agonists at receptors blocked by the parent compound. Thus, it is highly likely that these neuromodulations would counterbalance modafinil's cognitive enhancing properties.

The sparseness of studies only allows a descriptive analysis of the results and does not lead to definite conclusions. Further studies are needed to replicate the encouraging results described, and a meta-analysis necessary to quantitatively evaluate the advantageous effects of modafinil on cognitive, emotional and functional domains. Modafinil has been shown to be beneficial in all studies that showed a difference between placebo and the drug. At some future time, when there are sufficient studies which utilize similar dose levels and patient demographics, it may be possible to conduct a meta-analysis; but unfortunately this is not currently possible.

## 3. Mechanisms of action in the brain

As stated above, modafinil might act as a cognitive and emotional enhancer for people suffering from schizophrenia, thus ameliorating symptoms and leading to improvements in social and occupational functioning. However, little is known about the actions of modafinil in the brain despite a growing animal and human literature. Over 800 relevant publications yield disparate evidence and the only convincing summary of modafinil's functions in the brain has come from a review by Minzenberg et al. (2008), which specifically analyses the effects of modafinil on neurotransmitter function rather than taking a regional or neural systems approach. Thus, we have reviewed the literature in order to clarify the role of modafinil in specific brain regions, the changes in neurotransmission in these brain regions, and the interrelationship that may exist between these regions. PubMed electronic database was searched up until the end of April 2012 using combinations of the terms 'modafinil' and 'brain', 'cerebral', 'cortex', 'frontal', 'prefrontal', 'orbitofrontal', 'forebrain', 'temporal', 'parietal', 'occipital', 'cingulate', 'paracingulate', 'hippocampus', 'parahippocampus', 'hypothalamus', 'thalamus', 'amygdala', 'striatum', 'caudate', 'putamen', 'nucleus accumbens', 'globus pallidus', 'substantia nigra', 'basal ganglia', 'locus coeruleus', 'dorsal raphe' and 'limbic system',

and 'GABA', 'glutamate', 'dopamine', 'noradrenaline', 'adrenaline', 'serotonin', 'choline', 'acetylcholine', 'histamine', and 'orexin'. Studies providing data of modafinil's action on neurotransmitters in specific brain regions were included. Studies were excluded for the following reasons: studies only reporting an effect of modafinil on a neurotransmitter but not in a specific brain region or studies using a different compound than modafinil. Sixty studies fulfilling these criteria were identified. Table 3 shows the studies included in this review, by neurotransmitter and brain region studied. Details about the dosage and effect (increase, decrease or no effect) of modafinil are also provided, together with information about the species and some the neurotransmitter system studied.

### 3.1. Description of modafinil's action by neurotransmitter by brain region

#### 3.1.1. Global actions

Modafinil affects neurotransmitter function in many brain regions, including thalamus, hypothalamus, basal ganglia, substantia nigra, nucleus accumbens, caudate, hippocampus, ventral tegmental area, amygdala and several regions of the cortex. Following treatment with modafinil, neuronal activity has been detected in several of these regions and effects on the GABAergic, glutamatergic, dopaminergic, noradrenergic, serotonergic, histaminergic and orexinergic systems have been described. In all of the brain areas documented, the GABAergic system appears to be systematically down-regulated by modafinil, while other neurotransmitter systems seem to be up-regulated by the drug (Table 3).

#### 3.1.2. Actions of modafinil in the cortex

Increased neuronal activation has generally been identified with modafinil administration in several regions of the cortex in different animals, including mice, rats, cats and humans (Engber et al., 1998; Ghahremani et al., 2011; Gozzi et al., 2012; Hunter et al., 2006; Lin et al., 1996; Minzenberg et al., 2008; Pierard et al., 2007; Scammell et al., 2000; Urbano et al., 2007). Decreased neural activation has also been described in human studies when cognitive tasks were being performed (Minzenberg et al., 2011; Rasetti et al., 2010) or where the study was performed on individuals suffering from narcolepsy (Joo et al., 2008a), The cerebral cortex has shown increased levels of glutamate (Dawson et al., 2010; Touret et al., 1994), noradrenaline (de Saint Hilaire et al., 2001; Tanganelli et al., 1995; Wisor and Eriksson, 2005) and serotonin (de Saint Hilaire et al., 2001; Ferraro et al., 2005, 2000, 2002) following modafinil, whereas GABA appears to be down-regulated (Ferraro et al., 1997a, 1997b; Scammell et al., 2000; Tanganelli et al., 1992, 1995). The forebrain has shown effects of modafinil on dopamine and noradrenaline levels (Wisor and Eriksson, 2005).

With respect to the prefrontal cortex, where it might be supposed that many of the cognitive-enhancing effects of modafinil are mediated, the picture is generally the same as for cortex in general. Thus, it was observed that this region had increased levels of glutamate (Dawson et al., 2010), dopamine (de Saint Hilaire et al., 2001; Nguyen et al., 2011), noradrenaline (de Saint Hilaire et al., 2001) and serotonin (de Saint Hilaire et al., 2001; Ferraro et al., 2005). However, GABAergic modulation has not yet been reported in this region.

#### 3.1.3. Actions of modafinil in the hippocampus

Increased neuronal activity has also been observed in the hippocampus after modafinil administration, both in experimental animals and humans (Engber et al., 1998; Gozzi et al., 2012; He et al., 2011; Joo et al., 2008a; Kim et al., 2007; Pierard et al., 2007; Tsanov et al., 2010). Unlike the cerebral cortex, no studies have assessed the effect of modafinil on monoamines, histamine, or

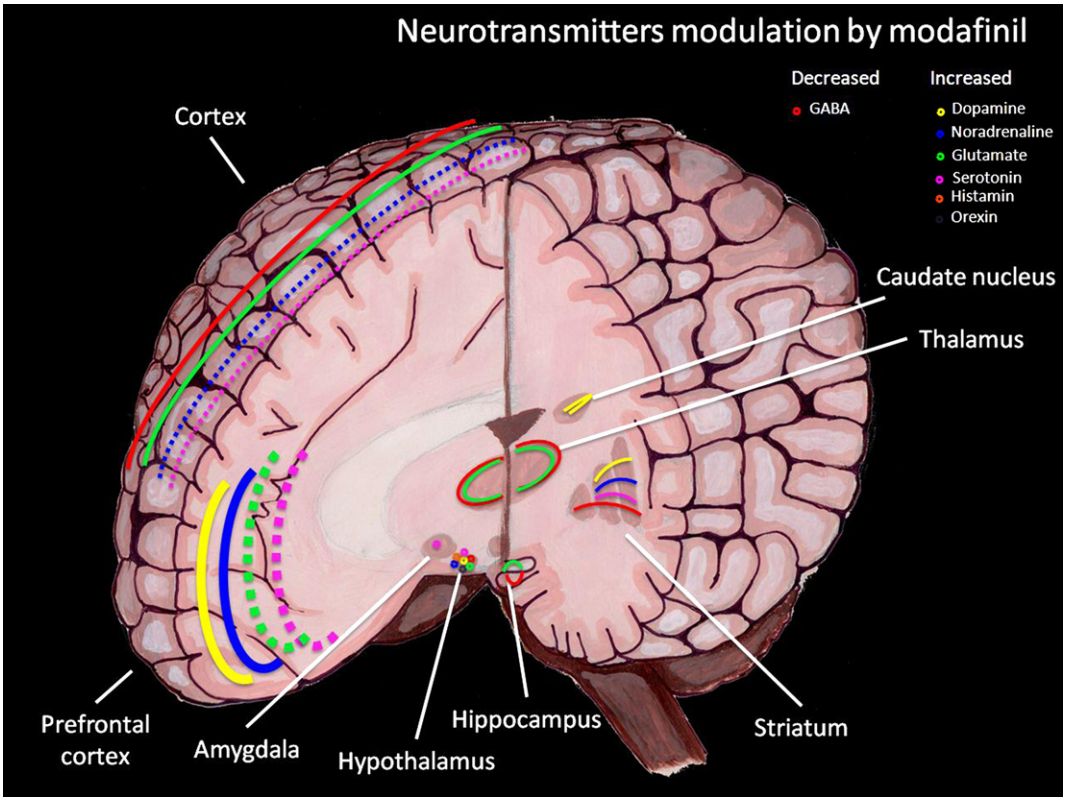


**Fig. 2.** Neurotransmitters modulation by modafinil in the brain.

orexin. However, glutamatergic neurotransmission appeared to be similarly increased by the drug (Ferraro et al., 1997a) and the GABAergic neurotransmission was decreased by the drug (Ferraro et al., 1997a; Huang et al., 2008).

*3.1.4. Actions of modafinil in the hypothalamus*

Neuronal activity was found in different regions of the hypothalamus (Arias-Carrion et al., 2011; Engber et al., 1998; Ishizuka et al., 2010; Lin et al., 1996; Murillo-Rodriguez et al., 2007; Pierard et al., 2007; Scammell et al., 2000) and this region of the brain had the largest number of neurotransmitters modulated by modafinil. Not only does it modulate the glutamatergic (Ferraro et al., 1999), GABAergic (Ferraro et al., 1997a, 1999, 1996; Scammell et al., 2000), noradrenergic (de Saint Hilaire et al., 2001) and serotonergic neurotransmission systems (de Saint Hilaire et al., 2001; Ferraro et al., 2002), but it also appears to activate the histamine (Ishizuka et al., 2008a, 2010, 2003) and the orexin (Chemelli et al., 1999; Rao and Shinde, 2009; Rao et al., 2007; Scammell et al., 2000) systems. Surprisingly, there is only one study that analysed the influence of modafinil on the dopaminergic system, with no statistically significant effects found (de Saint Hilaire et al., 2001).

*3.1.5. Actions of modafinil in the thalamus*

The thalamus had a similar pattern of activation compared to the hippocampus, i.e. increased neuronal activation (Engber et al., 1998; Gozzi et al., 2012; Urbano et al., 2007) and glutamate levels and decrease of GABA levels (Ferraro et al., 1997a). One study in monkeys showed that noradrenaline receptors were recruited by modafinil, but it is not known how these are regulated by the drug (Madras et al., 2006).

*3.1.6. Actions of modafinil in the basal ganglia*

*3.1.6.1. Amygdala.* The amygdala showed general increased neuronal activation (Engber et al., 1998; Lin et al., 1996; Pierard et al., 2007; Scammell et al., 2000) and one study showed decreased neuronal activation (Rasetti et al., 2010). Neurotransmitters have not been studied very thoroughly in this region of the brain. The serotonergic system has been found to be enhanced by modafinil administration in one rat study (Ferraro et al., 2002).

*3.1.6.2. Striatum.* Modafinil increased neuronal activity in the striatum (Gozzi et al., 2012; Lin et al., 1996; Scammell et al., 2000). It also increased levels of dopamine (Aguirre et al., 1999; Andersen et al., 2010; Fuxe et al., 1992; Madras et al., 2006; Nguyen et al., 2011; Ueki et al., 1993; Volkow et al., 2009; Wisor and Eriksson, 2005; Xiao et al., 2004), with one study showing that differential effects of modafinil were obtained, depending on the receptor targeted; D2 receptors were down-regulated by the drug and DAT and D1 receptors up-regulated (Nguyen et al., 2011). Modafinil increased noradrenaline and serotonin neurotransmission in one study (Xiao et al., 2004), whereas it decreased levels of GABA (Ferraro et al., 1997a, 1999, 1996; Scammell et al., 2000; Xiao et al., 2004). However, modafinil does not appear to have any effect in the glutamatergic system in this region of the brain (Ferraro et al., 1999; Xiao et al., 2004).

*3.1.6.3. Globus pallidus.* The globus pallidus only shows evidence of decreased levels of GABA after modafinil administration (Ferraro et al., 1999; Zeng et al., 2004).

*3.1.6.4. Substantia nigra.* Results are heterogeneous in this brain region. Some studies show increased activation of glutamate, GABA (Xiao et al., 2004) and dopamine (Fuxe et al., 1992; Jenner et al., 2000; Nguyen et al., 2011; Ueki et al., 1993; van Vliet et al., 2008) others show decreased activation (Ferraro et al., 1999; Korotkova et al., 2007), whereas some do not show any effect of the drug on these neurotransmitters (Akaoka et al., 1991; De Sereville et al., 1994; Ferraro et al., 1999; Korotkova et al., 2007). Thus, the pharmacomechanistic of modafinil remains to be determined in this brain region.

*3.1.6.5. Ventral tegmental area.* This region does not appear to be modulated by modafinil (Akaoka et al., 1991; Engber et al., 1998; Korotkova et al., 2007), although a recent study showed a correlation between the connectivity within the dopamine network projections from the ventral tegmental area to the nucleus accumbens (Gozzi et al., 2012).

*3.1.7. Actions of modafinil in the midbrain*

Certain regions localized in the midbrain have been shown to be modulated by modafinil administration. The locus coeruleus showed an increase in glutamate levels (Touret et al., 1994), however no noradrenergic changes have been observed (Akaoka et al., 1991). Under the combined influence of modafinil and fluoxetine, the selective serotonin reuptake inhibitor, the dorsal raphe serotonergic system is activated (Ferraro et al., 2005, 2002).

*3.2. From neurotransmitters in the brain to cognition and emotion: interpretation of how modafinil modulate these*

*3.2.1. Modulation of brain regions involved in cognition by modafinil*

How the effects of modafinil in different regions of the brain relate to different behavioural and cognitive effects of the drug is only slowly being unravelled. The interrelationship between different areas of the brain gives us clues about the neural functions modulated by modafinil and allow us to speculate about the mediation of the effects. Human studies have shown that modafinil administration is generally associated with increased cortical activation (Ellis et al., 1999) and prefrontal cortical activation in particular (Joo et al., 2008a, 2008b). Indeed, it has been postulated that modafinil's regulation of the dopaminergic, noradrenergic and serotonergic neurotransmitters in the prefrontal cortex (de Saint Hilaire et al., 2001; Ferraro et al., 2005, 2000; Tanganelli et al., 1995; Wisor and Eriksson, 2005) promotes arousal and cognition through ascending pathways that involve the hypocretin/orexin systems (Boutrel and Koob, 2004). MRI studies have attempted to unravel the effects of modafinil in the human brain associated with cognition. The administration of modafinil was associated with activation of cortical regions during the assessment of working memory, attention and executive tasks (Hunter et al., 2006; Minzenberg et al., 2008; Spence et al., 2005; Thomas and Kwong, 2006). However, these studies have generally failed to show the behavioural improvements of the drug that have been evident in studies that have not employed functional imaging.

*3.2.1.1. Modafinil and alertness.* Modafinil has been shown to improve attention (Dean et al., 2011). The thalamus and hypothalamus, and their interplay with the prefrontal cortex, control brain states associated with wakefulness (Purves et al., 2004), and it has been postulated that modafinil improves alertness and concentration via changes in the balance of neurotransmitter activity in these areas. Actions on adrenergic and dopaminergic receptors have been invoked in explaining the arousing actions of modafinil. Evidence for a role for dopamine rather than noradrenaline is provided by Wisor et al. (2001); DAT knock-out mice were insensitive to the arousing effects of modafinil. Moreover, profound noradrenaline depletion failed to reduce the wake-promoting effects of modafinil, as measured by REM sleep in mice

(Wisor and Eriksson, 2005). However, in the same study, the adrenergic alpha-1 receptor antagonist terozosin was effective in blocking wake-promoting effects of modafinilin the noradrenaline-depleted mice, suggestive of an agonist action of modafinil at adrenergic alpha-1 receptors. The histamine system also contributes to wakefulness (Lin et al., 1994) and it has been suggested that modafinil may act by promoting histamine release (Scammell et al., 2000). Indeed, neuronal activation is increased with the drug in the tuberomammillary nucleus (Scammell et al., 2000), which is the sole source of histamine in the brain (Benarroch, 2010). However, modafinil appears to be inefficient at modulating histamine in this region, although it does modulate it in an adjacent region, the anterior hypothalamus (Ishizuka et al., 2003). Circadian rhythms of histamine release from the anterior hypothalamus correlate positively with locomotor activity (Ishizuka et al., 2008b; Mochizuki et al., 1992). One possibility is that modafinil does not directly enhance attentional networks, but makes the circadian rhythms more regular. The body would hence receive top-down signals from neurotransmitter signalling in the thalamus, hypothalamus and prefrontal cortex related to daytime activity, which would make the individual believe he/she should not feel tired and should be concentrated and attentive, even though external cues (e.g. darkness) appear contradictory. Increases in neuronal activity have been observed with modafinil in the suprachiasmatic nuclei (Engber et al., 1998), which is the main cerebral region responsible for circadian mechanism (Hastings et al., 1998).

*3.2.1.2. Modafinil and working memory.* Modafinil has been shown to improve working memory in experimental animals (Pierard et al., 2007) and has also enhanced learning (Beracochea et al., 2002). The improvements induced by modafinil on working memory may reflect modafinil's action through catecholaminergic (Robbins and Arnsten, 2009) and glutamatergic pathways (Riedel et al., 2003). Working memory function is highly dependent on catecholamine neurotransmission in the prefrontal cortex (Robbins, 2005) and on glutamatergic and GABAergic neurotransmission in the hippocampus (Riedel et al., 2003). Modafinil might help to recruit more dopamine or noradrenaline in the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex, two brain regions involved in the recruitment, maintenance and processing of memorised items (Ungerleider et al., 1998). It may also improve memory encoding in the hippocampus by increasing levels of glutamate and decreasing levels of GABA. Thus, modafinil may act on these brain regions, hence promoting mnemonic functions.

*3.2.2. Brain regions involved in emotional regulation modulated by modafinil*

Modafinil induces neurotransmitter changes in many regions of the brain related to the limbic system (Engber et al., 1998; Scammell et al., 2000; Volkow et al., 2009), which might explain both its memory and mood enhancing properties. Tests of facial emotion recognition are sensitive to serotonergic modulation (Harmer et al., 2004), and pharmacological fMRI experiments indicate that selective serotonin reuptake inhibitors (Del-Ben et al., 2005; Murphy et al., 2009) modulate amygdala response to emotional faces. There is evidence that modafinil enhances neuronal activity in the amygdala (Engber et al., 1998; Lin et al., 1996; Scammell et al., 2000). Modafinil also has intriguing anxiolytic properties which have been linked to down-regulation of amygdaloid activations in human subjects undergoing fMRI (Rasetti et al., 2010). The neurochemical basis for this is unknown but may arise from possible effects of serotonin. Thus, modafinil increases serotonin levels when given conjointly with an SSRI such as paroxetine (Ferraro et al., 2000). This observation is evidently of potential therapeutic utility in the treatment of depression. However, it is not clear whether this activation is specifically associated with serotonergic neurons. The dopamine system also appears to be modulated by modafinil in the caudate nucleus, putamen, nucleus accumbens, and substantia nigra (Aguirre et al., 1999; Ferraro et al., 1997b; Fuxe et al., 1992; Jenner et al., 2000; Murillo-Rodriguez et al., 2007; Ueki et al., 1993; van Vliet et al., 2008; Volkow et al., 2009; Wisor et al., 2001; Xiao et al., 2004) but not in the globus pallidus, which appears to be modulated by GABA alterations (Zeng et al., 2004). A recent PET study in humans showed that modafinil prevents dopamine from binding dopamine transporters in the striatum, which induces increases in extra-cellular dopamine levels in this region of the brain (Volkow et al., 2009). However, modafinil has not been studied much in the context of emotional functions, so it is difficult to interpret the meaning of these enhanced activations in the limbic system. It is not entirely clear what aspects of modafinil's effects are mediated by its actions on the striatal dopamine system.

## 4. Conclusions

In this review we have shown that modafinil has the ability to improve cognitive and emotional functions both in healthy individuals and in patients with schizophrenia. The review also enables a better understanding of the neural mechanisms underlying these improvements. Modafinil improves cognitive function, in particular working memory, which appears to utilise dopaminergic and glutamatergic activity in the prefrontal cortex and hippocampus. Although several studies show modafinil's efficiency in targeting emotional functions, less is known how its emotional effects are mediated. The systematic neuronal activation and increase of glutamate, dopamine, noradrenaline and serotonin levels appears to be consistent, independent of the brain region considered. The same can be said for the decrease of GABAergic levels. However, the differential combination of neurotransmitters modulated by modafinil depending on the brain region is remarkable (Fig. 2).

However, it is important to consider that the summarised action of neurotransmitters in the brain results from converging work from both experimental animal and human studies. Therefore, there may be variations in the effects of modafinil depending on the animal model examined. Nevertheless, with the exception of human studies that analysed specific cognitive functions, studies appear to consistently show the same pattern of modulation by modafinil, regardless of the translational model.

This review is limited because was impossible to undertake a meta-analysis of the data; the sample were heterogeneous in terms of several factors, including behavioural tests and techniques employed. We excluded studies with armodafinil, the R enantiomer of the racemic compound modafinil, because variable ratios of R enantiomers could possibly lead to differential effects on cognitive function. Armodafinil has been claimed to be the active compound of modafinil, although a recent review on the effects of modafinil and armodafinil in patients with psychosis taking anti-psychotics fails to show an effect of armodafinil on cognitive function when taken chronically (Whittkampf et al., 2012). For conciseness, we did not compare the effect of modafinil with other central nervous system stimulants, such as methylphenidate and amphetamines. A descriptive review by Kim discusses the neural mechanisms and cognitive effects of amphetamine and caffeine and compares it to modafinil (Kim, 2012). Similar effectiveness was found. Nevertheless, a systematic review would enable more powerful answers to the differential effects of these compounds. It is important to note that multiple doses are necessary for each compound because of the variability in the dose response curves of the drugs.

Given the known associations between cognition and functional outcomes in schizophrenia, it is possible the improvement in cognitive functions induced by modafinil could have a significant beneficial effect on broader aspects of patients' functioning, including functional outcome, quality of life and wellbeing. In this respect, pharmacological cognitive enhancement in schizophrenia may be most beneficial if implemented early in the disorder, prior to chronic cognitive dysfunction and severe impacts on functioning and quality of life (Beddington et al., 2008; Sahakian et al., 2010). Modafinil may be particularly useful in the prevention of working memory impairments, which are present in people at high risk of psychosis who make the transition to frank psychotic disorder (Pukrop et al., 2007). A trial in this group is required. Improvement in working memory induces general cognitive and functional improvement, which ultimately may prevent the transition to psychosis. Modafinil may be equally efficient in healthy individuals, as it also have enhancing properties in this population.

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