European Neuropsychopharmacology (▮▮▮▮) ▮, ▮▮▮–▮▮▮

www.elsevier.com/locate/euroneuro

Modafinil combined with cognitive training: Pharmacological augmentation of cognitive training in schizophrenia

Panayiota G. Michalopoulou[a,*], Shôn W. Lewis[b], Richard J. Drake[b], Abraham Reichenberg[c,d], Richard Emsley[e], Anastasia K. Kalpakidou[a], Jane Lees[b], Tracey Bobin[a], James K. Gilleen[a], Gahan Pandina[f], Eve Applegate[b], Til Wykes[g], Shitij Kapur[a]

[a]*Section on Schizophrenia, Imaging and Therapeutics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, PO Box 053, 16 De Crespigny Park, London SE5 8AF, UK*
[b]*Institute of Brain, Behaviour and Mental Health, University of Manchester, UK*
[c]*Icahn School of Medicine, Mount Sinai, New York, USA*
[d]*Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK*
[e]*Institute of Population Health, University of Manchester, UK*
[f]*Janssen Research & Development, LLC, USA*
[g]*Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK*

Received 5 November 2014; received in revised form 20 February 2015; accepted 22 March 2015

KEYWORDS
Cognitive impairment associated with schizophrenia (CIAS);
Cognitive-enhancing drugs;
Modafinil;
Cognitive remediation;
Clinical trial;
Combination of cognitive-enhancing drugs with cognitive training

Abstract
Several efforts to develop pharmacological treatments with a beneficial effect on cognition in schizophrenia are underway, while cognitive remediation has shown modest effects on cognitive performance. Our goal was to test if pharmacological augmentation of cognitive training would result in enhancement of training-induced learning. We chose modafinil as the pharmacological augmenting agent, as it is known to have beneficial effects on learning and cognition. 49 participants with chronic schizophrenia were enroled in a double-blind, placebo-controlled study across two sites and were randomised to either modafinil (200 mg/day) or placebo. All participants engaged in a cognitive training program for 10 consecutive weekdays. The primary outcome measure was the performance on the trained tasks and secondary outcome measures included MATRICS cognitive battery, proxy measures of everyday functioning and symptom measures. 84% of the participants completed all study visits. Both groups showed significant improvement in the performance of the trained tasks suggesting potential for further learning.

*Corresponding author. Tel.: +44 20 748 0593; fax: +44 20 748 0287.
E-mail address: panayiota.michalopoulou@kcl.ac.uk (P.G. Michalopoulou).

http://dx.doi.org/10.1016/j.euroneuro.2015.03.009
0924-977X/

Please cite this article as: Michalopoulou, P.G., et al., Modafinil combined with cognitive training: Pharmacological augmentation of cognitive training in schizophrenia. European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.03.009

Modafinil did not induce differential enhancement on the performance of the trained tasks or any differential enhancement of the neuropsychological and functional measures compared to placebo. Modafinil showed no significant effects on symptom severity. Our study demonstrated that combining pharmacological compounds with cognitive training is acceptable to patients and can be implemented in large double-blind randomised controlled trials. The lack of differential enhancement of training-induced learning raises questions, such as choice and optimal dose of drug, cognitive domains to be trained, type of cognitive training, intervention duration and chronicity of illness that require systematic investigation in future studies.

1. Introduction

Cognitive impairment associated with schizophrenia (CIAS) is a strong predictor of the functional outcome of the illness (Green et al., 2000). CIAS is largely unaffected by antipsychotic medications (Keefe et al., 2007) and the therapeutic strategies targeting CIAS have either used pharmacological ("cognitive-enhancing drugs") or training approaches ("cognitive remediation"). The efforts to develop cognitive-enhancing drugs have met with limited success so far (Keefe et al., 2013), while a variety of cognitive remediation programs have shown modest effects on cognitive performance (Cohen's d=0.45) and functional outcome at follow-up (Cohen's d=0.37) (Wykes et al., 2011).

It has been suggested that training approaches in schizophrenia may need to be combined with pharmacological compounds that enhance learning in order to be optimally effective for CIAS (Michalopoulou et al., 2013). There is a wealth of evidence from animal studies showing that the combination of training with pharmacological compounds enhances training-induced learning (Floresco and Jentsch, 2011). In healthy humans amphetamine (Breitenstein et al., 2004), levodopa (Knecht et al., 2004) and modafinil (Gilleen et al., 2014) significantly enhanced the effects of training in an artificial language implicit learning task compared to placebo with retention of gains in task performance one month later (Breitenstein et al., 2004; Knecht et al., 2004). Ampakine CX516 combined with training in memory tasks significantly enhanced performance of the trained tasks compared to placebo (Ingvar et al., 1997). The combination of training with D-cycloserine (DCS) in anxiety disorders augmented the effects of training with some retention of efficacy at follow-up (Norberg et al., 2008).

In the present study we combined a cognitive training program with a cognitive-enhancing drug to test a therapeutic paradigm for CIAS. We investigated the potential of this combination to enhance training-induced gains on the performance of the trained tasks and secondarily we explored whether these gains would generalise in untrained cognitive tasks. Only two previous studies in schizophrenia have combined pharmacological compounds with cognitive training for CIAS and have used different design and outcome measures to our study: D'Souza et al. (2013) tested the effects of D-serine combined with a training program that targeted four cognitive domains on general cognitive measures and found no effects (D'Souza et al., 2013). Cain et al. (2014) combined an auditory training program with DCS and tested the effects of this combination on the performance of a trained auditory discrimination task and generalisation on untrained tasks (Cain et al., 2014). The study found significant learning effects on the trained auditory discrimination task, but no generalisation on untrained cognitive tasks.

In the present study we chose modafinil, a wakefulness-promoting drug, based on evidence from animal and human studies suggesting that modafinil may improve learning and cognition. In animal studies, modafinil accelerates learning of simple rules (Béracochéa et al., 2003), it reverses deficits in attentional set-shifting in phencyclidine-treated rats (Dawson et al., 2012), and it improves performance in spatial learning, working memory and sustained attention tasks (Béracochéa et al., 2002; Tsanov et al., 2010; Ward et al., 2004). In healthy, non-sleep deprived individuals, modafinil improves sustained attention (Randall et al., 2005), working memory and visual recognition memory, spatial planning and motor impulsivity (Turner et al., 2003), while it improves processing speed and divided attention in healthy individuals during simulated night-shift work (Hart et al., 2006). In children with attention deficit hyperactivity disorder (ADHD), modafinil improves attention functions and also executive functions, short- and long-term memory in adults with ADHD (Scoriels et al., 2013).

In schizophrenia, the effects of modafinil on training-induced learning have not been investigated yet, but some studies have investigated the effects of modafinil on cognitive measures: a single dose of modafinil improved verbal working memory and reduced the total number of errors in an attentional set-shifting task in chronic patients (Turner et al., 2004), it improved verbal working memory, spatial working memory errors and strategy use and reduced discrimination errors in a task testing impulsivity in patients with first-episode psychosis (Scoriels et al., 2012). Repeated administration of modafinil in a four-week open-label trial in chronic patients with schizophrenia improved working memory (Rosenthal and Bryant, 2004), while other chronic administration studies have not shown benefits of modafinil on cognition (Scoriels et al., 2013).

Modafinil has effects on multiple neurotransmitter systems: it inhibits dopamine (DAT) and norepinephrine (NET) transporters resulting in increased extracellular levels of dopamine and norepinephrine, it increases extracellular serotonin, glutatmate, histamine and orexin levels, while it decreases GABA levels (Minzenberg et al., 2008a). The pro-cognitive effects of modafinil are associated with its activity on DAT and NET in the prefrontal cortex (PFC), glutamatergic activity in the PFC and the hippocampus and GABAergic activity in the hippocampus (Scoriels et al.,

Please cite this article as: Michalopoulou, P.G., et al., Modafinil combined with cognitive training: Pharmacological augmentation of cognitive training in schizophrenia. European Neuropsychopharmacology (2015), http://dx.doi.org/10.1016/j.euroneuro.2015.03.009