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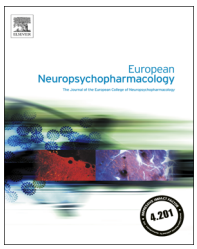

Modafinil combined with cognitive training is associated with improved learning in healthy volunteers – A randomised controlled trial ☆

J. Gilleen[a,*], P.G. Michalopoulou[a], A. Reichenberg[a], R. Drake[b], T. Wykes[a], S.W. Lewis[b], S. Kapur[a]

[a]*Institute of Psychiatry, King's College, London SE5 8AF, United Kingdom*
[b]*Institute of Brain, Behaviour and Mental Health, University of Manchester, United Kingdom*

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Abstract
Improving cognition in people with neuropsychiatric disorders remains a major clinical target. By themselves pharmacological and non-pharmacological approaches have shown only modest effects in improving cognition. In the present study we tested a recently-proposed methodology to combine CT with a 'cognitive-enhancing' drug to improve cognitive test scores and expanded on previous approaches by delivering combination drug and CT, over a long intervention of repeated sessions, and used multiple tasks to reveal the cognitive processes being enhanced. We also aimed to determine whether gains from this combination approach generalised to untrained tests. In this proof of principle randomised-controlled trial thirty-three healthy volunteers were randomised to receive either modafinil or placebo combined with daily cognitive training over two weeks. Volunteers were trained on tasks of new-language learning, working memory and verbal learning following 200 mg modafinil or placebo for ten days. Improvements in trained and untrained tasks were measured. Rate of new-language learning was significantly enhanced with modafinil, and effects were greatest over the first five sessions. Modafinil improved within-day learning rather than between-day retention. No enhancement of gains with modafinil was observed in working memory nor rate of verbal learning. Gains in all tasks were retained post drug-administration, but transfer effects to broad cognitive abilities were not seen. This study shows that combining CT with modafinil specifically elevates learning over early training sessions compared to CT with placebo and provides a proof of principle experimental paradigm for pharmacological enhancement of cognitive remediation.

☆Clinical Trial Registration: ISRCTN (Ref.: ISRCTN77185302). http://www.controlled-trials.com/ISRCTN77185302/.

*Corresponding author. Tel.: +207 848 0542; fax: +207 848 0287.
E-mail address: james.1.gilleen@kcl.ac.uk (J. Gilleen).

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1. Introduction

Cognition is impaired in a number of neurodevelopmental and neuropsychiatric disorders – schizophrenia being a classical example. These impairments contribute to poor functional outcomes (Green, 1996) and act as rate limiting factors for psychosocial interventions (Green et al., 2004). Accordingly, there is a strong need to develop methodologies that can reliably enhance cognitive functioning. Both non-pharmacological therapies (Dahlin et al., 2008a; Klingberg, 2010) and pharmacological compounds have been shown to improve a range of cognitive functions in healthy individuals (Husain and Mehta, 2011) as well as in neuropsychiatric populations such as schizophrenia (Barch and Carter, 2005; Harvey, 2009; Wykes et al., 2011), however, there have been only modest effects from these individual approaches.

Combining pharmacological and non-pharmacological methods may improve functioning beyond that achieved by either approach alone (Swerdlow, 2012) however, there are only a few controlled proof-of-principle studies in healthy volunteers or in patient samples, where a focus has been on addressing motor and language recovery after stroke. For example, L-dopa improves motor rehabilitation after stroke (Scheidtmann et al., 2001) and amphetamine enhances language learning in patients with post-stroke aphasia (Walker-Batson et al., 2001). Both of these compounds also elevate performance in an artificial language learning task in healthy volunteers when combined with repeated testing compared to placebo with repeated testing (Breitenstein et al., 2004; Knecht et al., 2004). Hence combining pharmacological compounds with task exposure or training, relative to combining with placebo, enhances functioning and may produce comparable effects in either promotion of recovery or elevation of functioning in healthy people relative to exposure to the functional component alone (or with placebo).

Modafinil, licensed for the treatment of narcolepsy and with wake-promoting action, has emerged as a possible agent to improve cognition. For example, it has been shown to improve cognitive function including memory, planning and attention in animals (Béracochéa et al., 2002; Morgan et al., 2007); reaction time, logical reasoning and short-term memory (Pigeau et al., 1995) working memory, planning and mental flexibility (Sugden et al., 2012) in humans following sleep deprivation; short-term memory, logical reasoning, spatial planning, vigilance, recognition memory performance in non-sleep-deprived healthy volunteers (see Repantis et al., 2010 for a review in healthy volunteers); and can improve cognitive functioning in clinical groups such as people with Attention Deficit Hyperactivity Disorder (Turner et al., 2004a) or cognitively-impaired drug-dependent participants (Kalechstein et al., 2010; Ghahremani et al., 2011). In schizophrenia, modafinil has also been shown to improve working memory and problem solving (Turner et al., 2004b; Scoriels et al., 2012). Therapeutically, if modafinil could improve cognitive functioning it may offer advantages over compounds such as amphetamine and L-dopa particularly if administration is required repeatedly over time as it is associated with low risk of abuse and has limited side-effects, which are well-tolerated and reversible (Minzenberg and Carter, 2008). While the precise mode of action of modafinil remains unclear it has effects on the monoamine system, especially the dopamine system (Madras et al., 2006; Volkow et al., 2009), the modulation of which is linked to cognitive effects.

This study serves as proof of principle trial to test the hypothesis that modafinil combined with cognitive training will produce greater improvements in performance on cognitive tasks in healthy participants compared to cognitive training with placebo; and also test if positive effects transfer to untrained tasks. The performance outcomes were scores on a series of tasks conducted daily for two weeks and this provided greater power to define trajectories of improvement. Investigating learning and cognition in healthy volunteers also constitutes an approach by which to develop an efficacious methodology to enhance cognition which is not confounded or obscured by disease or medication.

For the training task battery we chose several measures to target multiple cognitive processes: working memory (Dahlin et al., 2008a); implicit learning (Breitenstein and Knecht, 2002), and verbal learning (a variation of the California Verbal Learning Test; Delis et al., 1987). Working memory was trained with the Letter Memory (LM) task on which test scores show improvement with training in healthy young adults (Dahlin et al., 2008a, 2008b). Modafinil has been shown to improve working memory functioning in healthy participants (Turner et al., 2003) and normalise WM function in sleep-deprived healthy individuals (Bodenmann et al., 2009). The language learning task, a measure of implicit learning, also improves with training and is sensitive to pharmacological manipulations (Breitenstein and Knecht, 2002; Breitenstein et al., 2004; Knecht et al., 2004) and modafinil has been shown to improve associative learning in a single-dose design (Ghahremani et al., 2011). Lastly, verbal word learning performance also improves with repeat administration (Hawkins and Wexler, 1999; Gross et al., 2013) and is sensitive to show differences in performance improvements between those receiving memory training compared to a control condition (Gross et al., 2013). Short- and long-term memory are improved by modafinil in sleep-deprived healthy volunteers (Pigeau et al., 1995), as well as schizophrenia (Turner et al., 2004b). Thus, taken together we propose that these tasks are well suited to detect pharmacologically-assisted improvements over repeat administration with modafinil.

To date, there is mixed support for training gains transferring to untrained tasks (Dahlin et al., 2008b; Jaeggi et al., 2008), however, this has not been investigated with pharmacologically-enhanced learning. We thus further investigated whether performance gains generalised to untrained cognitive tests. Lastly we examined whether change in cognitive performance was modulated by IQ as has been suggested (Randall et al., 2005a, 2005b).

2. Experimental procedures

2.1. Design

A randomised, double-blind, placebo-controlled design was implemented. A two-arm design, previously used in several studies investigating the effects of compounds on cognitive function (Breitenstein et al., 2004; Knecht et al., 2004; Breitenstein et al., 2006) was adopted, whereby comparison of performance gains over