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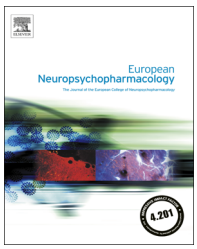

Modafinil combined with cognitive training is associated with improved learning in healthy volunteers – A randomised controlled trial ☆

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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/.

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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

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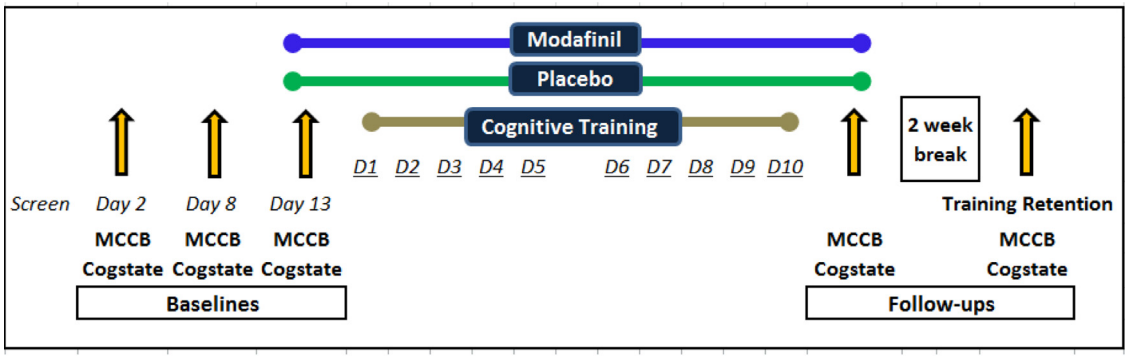

Fig. 1 Schematic of the study design, D=testing day, MCCB=MATRICS Consensus Cognitive Battery.

the ten training sessions in the CT+modafinil group could be made to those acquired in a CT+placebo group. Healthy participants were randomised (1:1 ratio) to receive a combination of modafinil, or placebo, with cognitive training (Fig. 1). Cognitive training comprised ten weekday sessions lasting 30 min each. To examine retention effects training tasks were administered again 2 weeks post-training. To examine transfer to untrained tasks the MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008) and Cogstate (Westerman et al., 2001) were administered before and after the ten cognitive training sessions. Two baseline measures were taken (B1 and B2) in line with clinical trial recommendations done to reduce variance due to task unfamiliarity (Buchanan et al., 2005).

2.2. Participants

2.2.1. Inclusion and exclusion criteria

The principal criteria were being 18-45 years old, able to read/write English to a sufficient level to understand and complete procedures (continued in Supplemental information S1). Participants were all resident in Greater London.

2.2.2. Recruitment and randomisation

Randomisation was performed independently by the Clinical Trials Unit, Institute of Psychiatry using a computerised minimisation procedure based on the variables: gender (M/F) and smoking (S/NS) to most likely produce balanced groups for these factors: gender, due to potential but unknown gender-related variation in response to modafinil; and smoking to balance the potential effects of nicotine (withdrawal and consumption) on cognition (e.g., Jacobsen et al., 2005). Written, informed consent was obtained from each patient. The study was carried out in accordance with the Declaration of Helsinki (World Medical Association declaration of Helsinki, 1997) and regulations of the locality in which the research was conducted. The study protocol and consent procedures were approved by the Moorfields and Whittington Research Ethics Committee (Ref.: 10-H0721-25) and registered with ISRCTN (Ref.: ISRCTN77185302).

2.2.3. Cognitive training tasks

The primary training task was the computerised Language Learning Task (LL; Breitenstein and Knecht, 2002) a measure of implicit learning. In each ten-minute session 400 auditory neologisms are paired with a pictorial object presented on a screen in a randomized order, presented as two blocks of 200 trials with 90-second break in-between. Stimuli pairs are delivered quickly to prevent overt conscious reflection (stimulus ISI=1.5 s: picture-sound co-presentation window=600 ms; response window 900 ms). Half of the trials consist of target paired words - the 50 word-picture combinations which are to be learnt - while the remainder is unpaired words. The pictures are schematic diagrams of everyday objects taken from the original research. Paired words occur twice as frequently per session as unpaired words, and this higher co-occurrence is the underlying learning principle. Unpaired words therefore receive the minimum co-occurrence - ten times fewer than the paired words over the training sessions. Participants are asked to press the 'y' or 'n' key according to whether they 'think the pair match or not' and the number of words learnt is defined by the percentage of correct 'hits' on paired words and 'rejections' of unpaired words. Participants are not told of the co-occurrence ratios nor that there are paired and unpaired words.

The secondary tasks are the Letter Memory (LM) and Verbal Learning tasks. The LM is a computerised, free recall, working memory task lasting 10 min (Dahlin et al., 2008a). Letters (A, B, C, and D) are serially presented (ISI=3: letter shown for 2 s, fixation for 1 s) in randomised lists of varied length (randomly selected lengths in each difficulty block: Easy: 4-7; medium: 5-11; hard: 6-15). Each presentation of a letter requires a mental 'update' of the list in working memory. Four correct trials in five presentations moves the participant to the next difficulty level in order to drive improvements. When the list ends participants are required to immediately (0 s delay) recall the four last letters seen. Scores represent the percentage of total number of updates completed from those presented. The Verbal Learning task (VL) consists of a list of 31 concrete words (categories: rooms, ornaments, animals, instruments, vegetables) read aloud at a rate of one every 2 s. After the last word participants are immediately asked to recall as many words as possible. All participants fully understood the tasks before testing. This was ensured verbally by the research administrators Table 1.

Table 1 Sample characteristics of the two groups.

	Modafinil ($N=15$)	Placebo ($N=18$)
Male:female	6:9	7:11
WASI IQ	109.8 (10.8)	110.5 (10.1)
Age (years)	28.7 (5.45)	29.7 (6.58)
Smoker: non-smoker	4:11	6:12

2.2.4. Intelligence

IQ was measured with the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999).

2.2.5. Transfer tasks

The MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein et al., 2008) and Cogstate (Westerman et al., 2001) are neuropsychological

test batteries measuring functioning in various cognitive domains. These batteries take approximately 1 hour each to complete and provide a total composite score. Both batteries can be given repeatedly over time and several of the tasks have alternate forms to reduce practice effects which were used in a counterbalanced fashion.

2.2.6. Investigational medicinal product

A dose of 200 mg/day of modafinil was chosen as it is consistent with previous studies in healthy individuals (Turner et al., 2003; Muller et al., 2004) and clinical populations (Turner et al., 2004b; Scoriels et al., 2013). Participants received a daily dose of modafinil or placebo approximately 2 h before training sessions as peak plasma concentrations occur 2–3 h after oral administration (Wong et al., 1999). Compliance of IMP consumption was prompted by telephone reminder, verified verbally at each visit, and a tablet count was conducted. Caffeinated drinks were prohibited before and during daily testing.

2.2.7. Secondary effects of modafinil

To account for physiological drug effects, a daily Alertness Questionnaire was administered (15 items; factors: attention-motivation, anxiety-stress, and sleep quality) and blood pressure and heart rate were measured before training. Participants were also asked daily about side-effects, and also a single question asking "*How sure are you out of 100% that you are taking the active compound?*" Lastly, the Cogstate Card Identification (ID) task provided reaction time performance pre- and post-training – participants must press a key as fast as possible when an on-screen playing card is turned over.

2.2.8. Analysis

The primary outcome measures were the change in performance on the three training tests at day 10 (D10) compared to day 1 (D1). Repeated-measures ANOVA were conducted to investigate between-group differences in cognitive performance change over the ten training days (training period; D10-follow-up comparison) as well as between-group differences on alertness, cardiac measures and ratings scales. *T*-tests were used to determine within-day differences in performance, while paired *t*-tests were used to show within-group change between time-points. Additionally, LL sessions consisted of two blocks of trials so repeated-measures ANOVA were used to investigate learning across blocks within-session, and retention from the second block of one day to the first block of the next day. Area-under-the-curve analyses were conducted to examine group differences in learning gains and retention, and Growth Curve Modelling was conducted to extract growth rate coefficients to characterise and test for group differences in rate of learning.

Analyses of responding on the LL were conducted post-hoc to examine possible drug-response biases. Correlation analyses revealed the relationships between change in training task performances and IQ. The secondary outcome measures were the change in untrained task performance from pre to post-training (MCCB MATRICS and Cogstate). To investigate transfer to the untrained tasks repeated-measures ANCOVA (baseline score as covariate) were used to examine group differences in MCCB and Cogstate composite score change.

3. Results

3.1. Sample characteristics

Of 80 participants who consented to take part 28 were excluded at screening mostly for medical reasons such as irregular ECG or high blood pressure, and 52 people were randomised into the study. Thirteen participants dropped out (mostly for having 'other commitments', or 'without reason'). Of the 39 who started the training phase, three participants dropped-out (reasons: 'new job', 'exam stress', 'other commitments') and three were excluded due to high BP (modafinil=1, placebo=2). Of the thirty-three completers, fifteen participants were randomised to the modafinil group, and eighteen to the placebo group. Only data from completers is shown. The groups were balanced in terms of IQ, gender, smoking status, and age.

3.2. Cognitive training

3.2.1. Language learning

The groups had similar percentage accuracy scores on the first day of training ($t(31)=.44$, $p=.66$). Over the training analyses revealed a significant effect of day ($F(9,23)=9.07$, $p<.001$) but not of group on performance accuracy. However, there was a statistically significant group by time interaction over the training sessions ($F(9,23)=2.45$, $p<.05$, $\eta 2=.49$; illustrated in Fig. 2A). The modafinil group showed faster improvement early in the training period and maintained its superior performance throughout the remaining assessments. LL scores were significantly greater at Follow-up (FU) compared to day one (D1) in both groups (both $p<.001$) indicating gains were retained. There was no group x time interaction for degree of decline from day ten (D10) to FU ($F(1,31)=.2$, $p=.65$).

Improvements were not attributable to a drug response bias as the modafinil group did not show an elevated propensity to just press the 'paired' response button more (greater false-positives). Number of 'paired' responses increased for the paired words particularly in the modafinil group, but 'paired' responses to unpaired words did not significantly change over time but were consistently low in both groups over the ten days (see Fig. 3). The frequency of 'paired' response to unpaired stimuli was numerically better in the modafinil group but repeated-measures ANOVA confirmed there were no effects of time ($F(9,23)=1.65$, $p=.15$), group ($F(1,23)=.036$, $p=.85$), nor a group by time interaction ($F(9,23)=1.08$, $p=.41$) of 'paired' response frequency to unpaired words.

3.2.2. Learning and retention

Within-day learning gains and between-day retention – are shown in Fig. 4. Over the first half of the training sessions, within-day cumulative learning, as measured by area-under-the curve, was significantly greater in the modafinil group compared to placebo (modafinil=24.7, placebo=12.3); $t(1,31)=2.04$, $p<.05$, ES=.84(95% CI=.01–1.42), whereas retention decay over the intervening day was not significantly different between the two groups ($t(1,31)=1.14$, $p=.26$). A post-hoc repeated-measures ANOVA confirmed significantly greater learning in the modafinil group was apparent over just the first 5 days ($F(1,31)=2.59$, $p<.05$, quadratic term).

3.2.3. Learning rate differences

Growth Curve Models revealed significantly greater quadratic coefficients in the modafinil group compared to the placebo group ($t(31)=2.68$, $p<.05$), ES=.75 (95% CI=.01-1.42).

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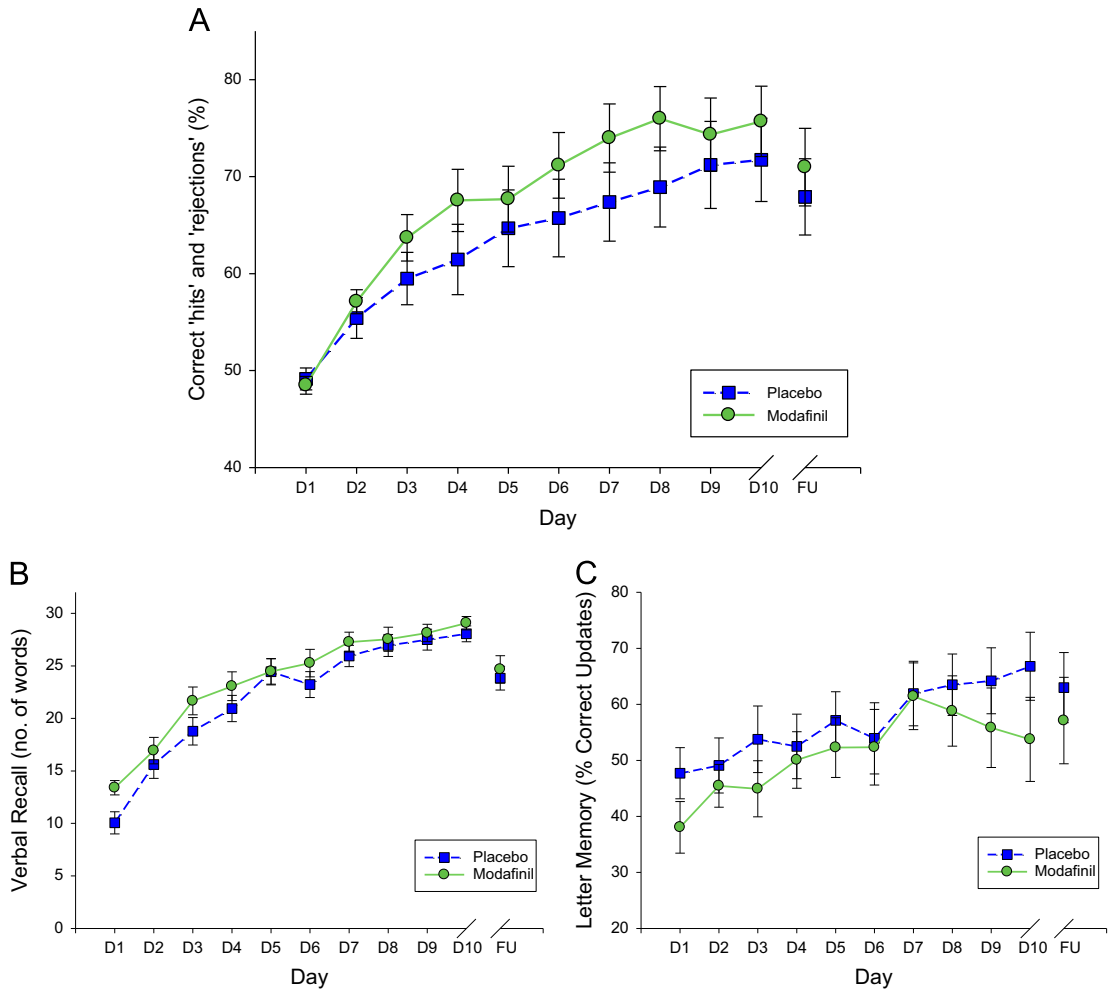

Fig. 2 Language learning (A); verbal learning (B); and letter-memory (C) scores for the placebo and modafinil groups over the ten training days, and performance at the two-week follow-up.

3.2.4. Verbal learning task

Both groups showed similar learning curves in VL immediate word recall (Fig. 2B) yet performance on D1 was significantly greater in the modafinil group than the placebo group ($t(31)=2.54$, $p=.008$). Higher scores on subsequent days did not reach significance. There was a significant effect of time ($F(9,31)=162.5$, $p<.001$), but not of group ($F(1,31)=1.24$, $p=.27$) and no significant group by time interaction ($F(9,31)=1.37$, $p=.28$, $\eta 2=.34$). Verbal recall totals by D10 and FU were higher in the modafinil group than placebo but this difference was not significant. VL scores were significantly greater at FU compared to D1 in both groups (both $p<.001$) indicating gains were highly retained. There was no group-$\times$time interaction for decline from D10 to FU ($F(1,31)=.20$, $p=.88$).

3.2.5. Letter-memory task

There were no statistically significant differences in D1 scores on the Letter Memory (LM) task ($t(31)=1.40$, $p=.17$), nor at D10, FU or any other training days (see Fig. 2C). There was a main effect of time ($F(9,31)=14.13$, $p<.001$) but not of group ($F(1,31)=.69$, $p=.41$), and no significant group by time interaction ($F(9,31)=.92$, $p=.53$, $\eta 2=.28$). LM scores were significantly greater at FU compared to D1 in both groups (both $p<.001$) indicating gains were highly retained. There was no significant difference in change from D10 to FU between the groups.

3.2.6. IQ and training performance

IQ scores were very similar in the two groups, yet IQ scores in the modafinil, not placebo group were strongly correlated with change in LL scores (D1–D10; $r=.74$, $p<.005$), and D10 VL ($r=.78$, $p<.005$) scores, and showed a strong trend to be associated with D10 LM scores ($r=.51$, $p=.054$). In the placebo group IQ scores did not correlate with D1, end-point or performance change scores.

3.2.7. Transfer effects to untrained tasks: MCCB and Cogstate

Repeated-measures ANCOVA revealed no significant between-group differences at any assessment point on the MCCB MATRICS or Cogstate composite scores, nor in the change in composite scores between any time points (all $p>.05$; composite scores shown in Fig. 5a and b below).

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Further *post hoc* analyses were conducted to investigate repeated-measures between-groups effects on MCCB subtests subsequent to, and controlling for, baseline. No significant group x assessment effects on test score were observed (all $p>.20$). A final *post hoc* analysis was conducted to investigate the relationship between change on the LL task from D1 to D10 and change in MCCB composite and subtests over the same period. There were no significant correlations in either group or across all participants (all $r<.30$, $p>.15$).

3.2.8. Secondary effects of modafinil

There were no significant between-group differences on mean daily alertness scores, nor were there main effects of time, nor group, nor interactions of time and group on total or factor scores (attention-motivation, anxiety-stress, and sleep quality) (all n.s.). There were no between-groups differences in reaction time change from pre- to post-training. Side-effects are reported in Supplemental information S2.

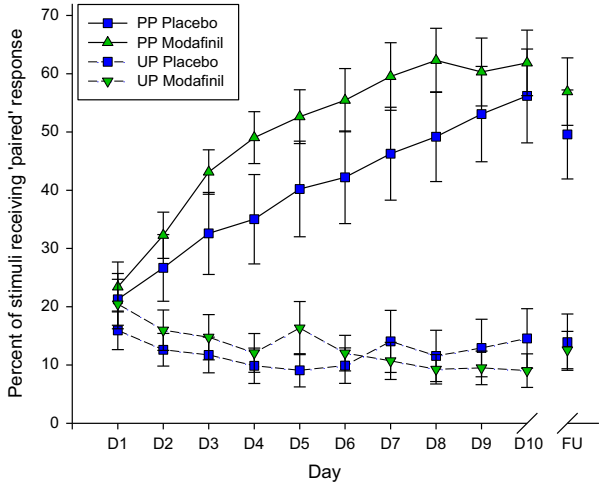

Fig. 3 Increase in 'paired' responses to true pairs (PP) and decreases of 'paired' responses to false-pairs (UP) over the ten training days.

3.2.9. Subjective judgement of modafinil vs. placebo assignment

At D1 guesses as to medication-assignment in each group (placebo or modafinil) were broadly at chance and not significantly different (modafinil group were 54.5% sure of taking modafinil vs. 42.5% in the placebo group; $t(31)=1.65$, $p>.05$). There was a trend for those in the modafinil group to be more sure of being on modafinil at D10 compared to the placebo group ($t(1,31)=1.95$, $p=.06$). The modafinil group were still scoring near chance (47% surety), but the placebo group became more sure of not being in the modafinil group (32% surety of being on modafinil).

3.2.10. Blood pressure and heart rate

Sitting diastolic, standing systolic and heart rates values were not significantly different between the two groups, but sitting systolic ($F(1,22)=7.76$, $p<.05$), and standing diastolic blood pressure ($F(1,22)=3.02$, $p<.05$) were elevated in the modafinil group compared to the control group.

4. Discussion

Combining cognitive training with modafinil administration over multiple sessions enhanced cognitive performance significantly more than placebo with cognitive training, as hypothesised, although this effect was specific to implicit associative learning (LL task). Enhancement of performance in the Language Learning task by modafinil, driven by within-day gains in learning rather than better retention, was evident within even the early days of training, and gains were durable after the cognitive training ceased. Verbal learning performance was also significantly greater in the modafinil group at first presentation. These effects suggest that modafinil may act specifically to enhance learning mechanisms. Whilst gains were seen on all training tasks improvements did not generalise to the untrained tasks in either group.

The critical observation is that significant increases in learning rates were observed in the modafinil group in the language learning task. The positive effects of modafinil over the ten training sessions (approximately an extra 5% LL accuracy gain on 22% accuracy in the placebo group, equal to ten additional words on 70 words learnt) are comparable,

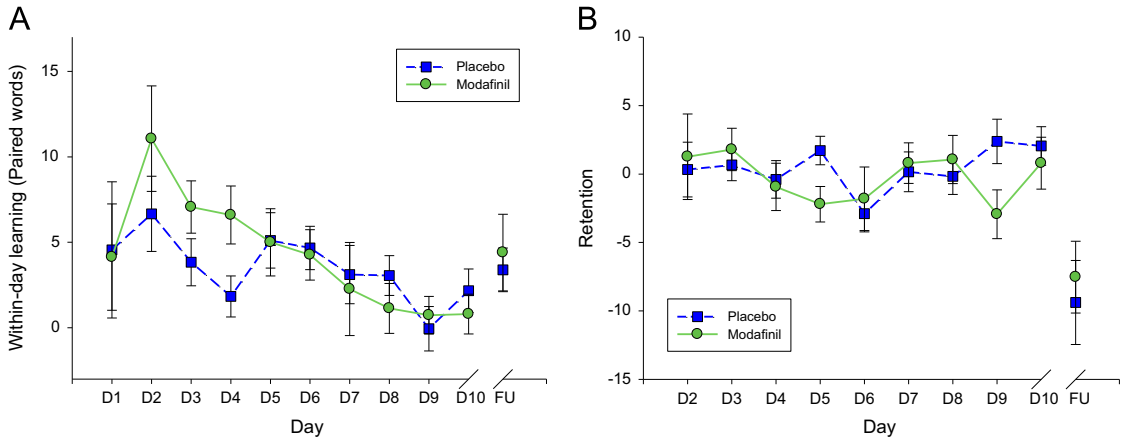

Fig. 4 Gains in words learnt from the first to the second block in each testing session (A), and retention scores on the first block of each day compared to the last block of the previous day.

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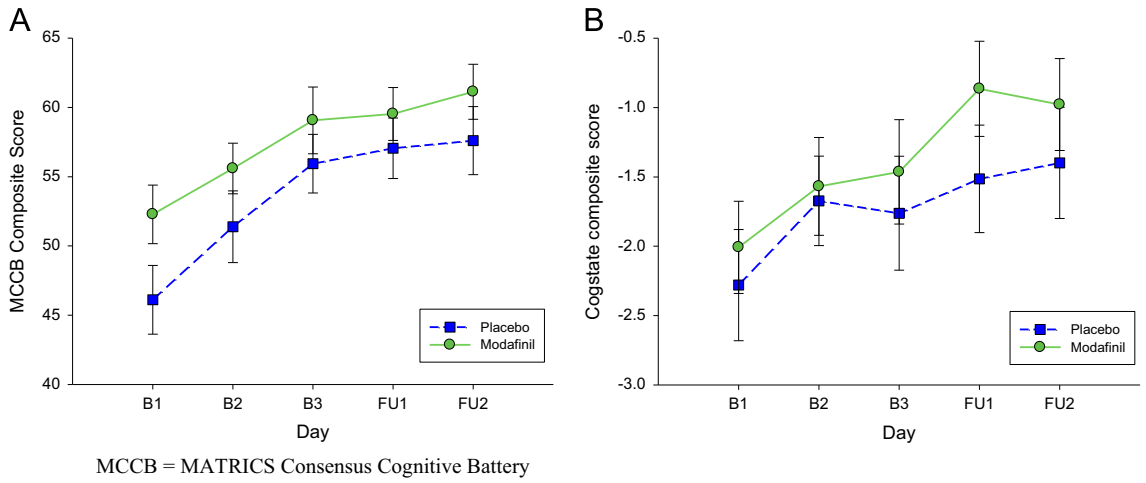

Fig. 5 MCCB MATRICS composite scores (A) and cogstate composite scores (B) at each assessment session (B1, B2 and FU2 are off-drug; B3 and FU1 are on-drug) MCCB=MATRICS Consensus Cognitive Battery.

if a little lower, to those seen previously with amphetamine (~10% on ~30% gains (Breitenstein et al., 2004)) and L-dopa (~6% on ~35% gains (Knecht et al., 2004)) albeit over a different time frame. Absolute gains made after ten training days in the placebo group were already achieved by day five in the modafinil group, by which time the modafinil group made approximately 25% greater gains in percentage accuracy than the placebo group, and 37% by day 6. The differences on the final day of training are less striking as the placebo group 'caught-up' as performance in the modafinil reached a plateau. Modafinil may therefore specifically affect early learning or it may be that task-specific ceiling effects limit the potential gains of the modafinil group.

Modafinil selectively enhanced within-day gains not between-session retention indicating that it is during an active state of learning – during task delivery – rather than post-task consolidation where modafinil's action may lie. Indeed, this specific effect of modafinil to improve learning but not retention has previously been demonstrated in mice (Shuman et al., 2009). Importantly, gains in the modafinil group were not attributable to a drug response bias – 'paired' responses became more discriminatory for both paired (more) and unpaired (fewer) words – nor attributable to greater generalised physiological or subjective drug effects.

Performance scores on the verbal learning task were also consistent with a positive effect of modafinil on learning. Between-group differences were highly significantly different on day one when first exposure to the word-list requires greater learning relative to subsequent days due to list novelty. Group differences were no longer apparent on subsequent presentations when relative learning requirements diminish; with daily gains there are fewer words left to learn. Conversely, on the LL task, differences were not apparent on day one and indeed negligible learning is possible in the first session due to the similar ratio of paired to unpaired words. L-dopa (Knecht et al., 2004) and amphetamine (Breitenstein et al., 2004) also do not produce day 1 differences on the LL task compared to placebo. Learning potential only rises in subsequent sessions when the ratio of paired to unpaired words (the learning signal) increases, and indeed it was during these sessions that the effect of modafinil was observed. LL performance gains were not linked to working memory performance as working memory was not significantly improved by modafinil.

The effect of modafinil on learning is consistent with previous work showing that modafinil facilitates learning in mice (Béracochéa et al., 2002, 2003; Shuman et al., 2009), and also in humans (Hart et al., 2006; Makris et al., 2007). Hart et al., for example, report significantly improved night-shift-related deficits on a motor sequence learning task (Hart et al., 2006). In schizophrenia patients, Scoriels et al. (2012) found a significant order effect within a cross-over design by which cognitive performance was greater when modafinil was taken in the second session (compared to first) which also suggests that modafinil improves performance with repeat task exposure. Despite this, other studies in schizophrenia (e.g., Sevy et al., 2005; Pierre et al., 2007; Freudenreich et al., 2009; Scoriels et al., 2012), healthy volunteers (e.g., Turner et al., 2003; Ghahremani et al., 2011) and methamphetamine-dependent participants (e.g., Kalechstein et al., 2010; Ghahremani et al., 2011) that have used learning measures have generally not shown modafinil-related improvements. However, these studies assessed learning in a single active compound test-session (cross-over single dose or change over adjunct period designs). This has been improved upon in the current study where learning relates to the more canonical concept of acquisition of skill or knowledge over time and is, therefore, a more ecologically-valid investigation of learning.

The specificity of the effects of modafinil to learning (and not VL or LM) is intriguing. Whilst there are clear cognitive and neural differences in the foundations of these tasks, it is challenging to integrate this profile of effects into a fuller neurobiological account. This is because of a lack of clarity over the effects of modafinil – which may have direct, indirect and interactive effects in multiple neurotransmitter systems. Future studies should aim to take neurobiological measures to investigate specificity of effects further.

Modafinil, as well as L-dopa and amphetamine, may however elevate learning on the LL task because these compounds selectively increase phasic dopamine (DA) transmission. Pergolide, a DA agonist, which *tonically* stimulates dopamine receptors, *decreases* LL performance (Breitenstein

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et al., 2006). While modafinil's neurobiological actions are non-specific, evidence suggests that modafinil blocks DA transporters (Volkow et al., 2009) and elevates dopaminergic transmission (Minzenberg and Carter, 2008). Hence it is plausible that modafinil's effects may be via the DA system, which is consistent with known effects of dopamine on associative learning (Schultz et al., 1997). Modafinilsignificantly improves associative learning in methamphetamine-dependent volunteers who have low dopamine functioning (Ghahremani et al., 2011) potentially due to effects on striatal DAT availability and dopamine levels. In the same study, healthy volunteers did not significantly improve but this was attributed to a ceiling effect. Of course, within the LL task there may be fractionable sub-processes which are specifically targeted by modafinil. Effects appear to be on learning rather than retention, but within the learning process many cognitive elements are in operation – information-processing, verbal and visuo-spatial cognition, processing stimuli contingency across modalities, and the unlearning of previously irrelevant stimuli to mention just a few. Future work should examine the neurobiological bases of these tasks and sub-processes, and of modafinil itself in order to fully understand the specificity of effects.

The effects of modafinil given over multiple sessions with CT are specific and modest, however, this mirrors the evidence from acute-dose designs for the pro-cognitive effects of modafinil. The majority of positive findings relate to normalisation of impaired function in sleep-deprived healthy volunteers (see Repantis et al., 2010), or in preventing cognitive deterioration over time (e.g., Makris et al., 2007). Studies of modafinil in non-sleep deprived healthy volunteers (e.g., Turner et al., 2003; Muller et al., 2004, 2013; Randall et al., 2003, 2005a, 2005b) provide a mixed account of positive and negative effects across different domains of functioning (for example working memory), or effects on specific conditions within a task but not others. The rationale for the design of the present study was precisely to promote effects by combining modafinil with cognitive training.

Among the limitations of our study we acknowledge the relatively small number of participants and high score variability, yet this was a proof of principle study conducted to investigate the potential of modafinil to enhance cognitive training performance. Significant drug effects on the implicit learning task (Knecht et al., 2004; Breitenstein et al., 2006) and significant effects of modafinil on cognitive tests in acute dose studies have been previously demonstrated with similar participant numbers (see Scoriels et al., 2013 review) but studies with larger participant numbers are both warranted and required. The small sample size precluded further investigation of subgroups but differential effects of modafinil on cognition may be apparent in participants who differ genetically (Bodenmann et al., 2009), or with respect to baseline function (e.g., Muller et al., 2004). Although groups were balanced for age there was a broad age range. There is evidence that age may moderate effects of cognitive training (Dahlin et al., 2008b) so future studies should aim to recruit participants from a narrower range or increase the sample size so this can be explicitly investigated.

No transfer effects were observed in the untrained test battery. The MCCB, which is FDA-approved for use in clinical trials for cognition in schizophrenia and shows sound psychometric properties (Buchanan et al., 2010), may not be sufficiently sensitive to detect drug-effects either in schizophrenia (e.g. Deutsch et al., 2013) or healthy volunteers (Chou et al., 2013). For example, no significant changes in MCCB composite and domain scores were observed in healthy volunteers following 20 mg amphetamine administration (Chou et al., 2013). However, there was also a lack of transfer effects on the Cogstate test battery hence lack of transfer effects may be due to the lack of specificity of drug effects.

The length of the training period was ten days which was deemed suitable given previously demonstrated drug-effects on the LL task over this period (Breitenstein et al., 2004; Knecht et al., 2004). This duration also reduced the potential psychometric challenge of ceiling effects which would be more likely over a longer training intervention. Wykes et al. (2011) have previously recommended a 40-day period of CRT intervention for clinical benefit but shorter interventions within a proof of concept trial is more practical and was considered appropriate to the study aims.

The study used a two-arm design and a potential criticism is that additional experimental conditions are needed for valid inferences to be made. However, we propose this is not in fact the case given the purpose of the trial was to investigate effects on cognitive performance throughout the daily training intervention. Firstly, a drug-alone condition cannot be included as the administration of CT tests, required to measure performance, would constitute a CT component in the first instance. Further our cognitive measures have previously each demonstrated reliable and significant gains due to repeat administration alone, hence our interest was not to assess the efficacy of repeat administration of these tasks to enhance performance per se. To investigate whether modafinil may elevate CT gains a CT plus placebo arm forms an appropriate baseline against which performance of a modafinil plus CT arm can be compared.

While modafinil may produce less striking (or more varied) learning rate gains than L-dopa or amphetamine, it may be preferable as it may result in fewer potential health risks than L-dopa and amphetamine, specifically if applied to patient groups such as schizophrenia where raising dopamine transmission may exacerbate psychosis. Indeed, we propose that positive effects on cognition may support the possibility of transfer of this methodology to patient groups, such as schizophrenia, where cognition in these domains is impaired. However, it may be that differences in developmental and neurobiological factors as well as obvious differences in cognitive status and medication may mean that comparable effects may not occur. Despite this, strong similarities of effects of modafinil in patient and healthy groups have been demonstrated (Turner et al., 2003; Turner et al., 2004b) as well as in healthy and patients groups in other domains of functioning with amphetamine (Barch and Carter, 2005) and also directly on functioning in the same domain as shown, for example, with amphetamine and L-dopa on language learning in healthy and patient groups (Scheidtmann et al., 2001; Walker-Batson et al., 2001; Breitenstein et al., 2004; Knecht et al., 2004).

In conclusion, this study is the first to show that modafinil enhances cognitive performance, specifically early learning,

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in healthy participants compared to placebo with repeated cognitive training. Modafinil afforded gains in learning which were particularly available over the very first sessions hence patient groups with learning difficulties may benefit from this approach. The short intervention time needed for learning effects to emerge provides potential therapeutic advantage in clinical settings where time and financial costs may be constrained. As retention is relatively flat between sessions and within-session gains are significant, future work should seek to investigate how frequently learning sessions can be delivered. Sessions delivered in close temporal proximity may confer greater gains, or similar gains over a much shorter time. It remains a major clinical target to find robust methodologies to improve cognitive and functional outcomes in patient groups. We propose that this combination approach should be undertaken in neuropsychiatric populations. Whilst these data do not point to a cognitive panacea, modafinil may offer the potential to enhance learning with low risk of side-effects and abuse; and unlike amphetamines and L-dopa, may be more realistically used therapeutically.

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Contributors

All authors contributed to development of the study design. JG coordinated the study, wrote the draffs and subsequent edits, also conducted analyses, literature searches. AR contributed time for analyses; AR and SK both provided additional content. YM, RD, TW, SL provided suggestions for amendments. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors disclose no conflicts of interest in relation to the present study. JG, YM, AR, RD have no conflicts of interest to report. SL has research funded by the MRC. He has received funding for advisory work by NICE and by Abbott and Janssen-Cilag pharmaceuticals. SK has financial associations with: (Grant Support) AstraZeneca, Bristol-Myers Squibb, Glaxo Smith Kline; and has had consultant/scientific advisor/speaking engagements with AstraZeneca, Bioline, Bristol Meyers Squibb, Eli Lilly, Janssen (Johnson and Johnson), Lundbeck, NeuroSearch, Otsuka, Pfizer, Roche, Servier, and Solvay Wyeth. TW has had speaking engagements and consultancy with Lunndbeck and Bristol Myers Squibb.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.euroneuro.2014.01.001.

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