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The effects of modafinil on cognitive training: A Proof of Concept trial in patients with schizophrenia

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Abstract:	Background: The optimal therapeutic approach for cognitive impairment in schizophrenia may require a combination of cognitive remediation with pharmacological compounds that enhance learning. Our goal was to test the feasibility and learning effects of such a combined intervention in patients with schizophrenia. Methods: 49 participants with chronic schizophrenia or schizoaffective disorder were enrolled in a double-blind, placebo-controlled study across two sites and were randomised to either modafinil (200mg/day) or placebo. All participants engaged in a cognitive training program for 10 consecutive weekdays. The primary outcome measure was the performance on the cognitive training tasks and secondary outcome measures included neuropsychological measures (MATRICS Consensus Cognitive Battery), proxy measures of everyday functioning and symptom measures.

	Results: 84% of the participants enrolled in the trial completed all study visits. There was a main effect of time on all cognitive training tasks across the combined treatment groups. Modafinil did not induce differential enhancement in the performance of the trained tasks nor on the neuropsychological, functional capacity and symptom measures compared to placebo. Conclusions:Interventions combining pharmacological compounds with cognitive training are feasible in schizophrenia. Repeated doses of modafinil did not augment training-induced learning in chronic patients with schizophrenia and did not improve general cognitive performance. The interventions that combine training with pharmacological compounds for learning and cognitive impairment have just started to be explored in schizophrenia and issues such as choice of drug, chronicity of illness, cognitive domains to be trained and cognitive outcome measures require further investigation in future studies.

The effects of modafinil on cognitive training: A Proof of Concept trial in patients with schizophrenia

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Abstract

Background The optimal therapeutic approach for cognitive impairment in schizophrenia may require a combination of cognitive remediation with pharmacological compounds that enhance learning. Our goal was to test the feasibility and learning effects of such a combined intervention in patients with schizophrenia.

Methods 49 participants with chronic schizophrenia or schizoaffective disorder were enrolled in a double-blind, placebo-controlled study across two sites and were randomised to either modafinil (200mg/day) or placebo. All participants engaged in a cognitive training program for 10 consecutive weekdays. The primary outcome measure was the performance on the cognitive training tasks and secondary outcome measures included neuropsychological measures (MATRICS Consensus Cognitive Battery), proxy measures of everyday functioning and symptom measures.

Results 84% of the participants enrolled in the trial completed all study visits. There was a main effect of time on all cognitive training tasks across the combined treatment groups. Modafinil did not induce differential enhancement in the performance of the trained tasks nor on the neuropsychological, functional capacity and symptom measures compared to placebo.

Conclusions Interventions combining pharmacological compounds with cognitive training are feasible in schizophrenia. Repeated doses of modafinil did not augment training-induced learning in chronic patients with schizophrenia and did not improve general cognitive performance. The interventions that combine training with pharmacological compounds for learning and cognitive impairment have just started to be explored in schizophrenia and issues such as choice of drug, chronicity of illness, cognitive domains to be trained and cognitive outcome measures require further investigation in future studies.

Clinical Trial Registration: ISRCTN60687844 (www.isrctn.org)

Keywords: Cognitive Impairment Associated with Schizophrenia (CIAS), Pharmacologically Augmented Cognitive Therapies (PACT), cognitive-enhancing drugs, cognitive remediation, clinical trial

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.* 2011), while a variety of cognitive remediation programs have shown modest effects on cognitive performance (Cohen's d=0.45) and functional outcome (Cohen's d=0.36) (McGurk *et al.* 2007, 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 (Goff, 2012, Michalopoulou *et al.* 2013, Swerdlow, 2011). Evidence from animal studies suggests that the combination of training with pharmacological compounds enhances training-induced learning. In healthy individuals, compounds such as amphetamine, enhance motor learning leading to faster development, increased magnitude, and longer lasting duration of effects compared to placebo (Floresco and Jentsch, 2011). Amphetamine (Breitenstein *et al.*, 2004) levodopa (Knecht *et al.* 2004) and modafinil (Gilleen *et al.* 2014) enhance the effects of training in an artificial language implicit learning task. The combination of training with D-cycloserine (DCS) in anxiety disorders augments the effects of training (Norberg *et al.* 2008). In schizophrenia, the combination of pharmacological compounds that enhance learning with cognitive training and the effects of the combination on learning and cognition have just started to be explored: The combination of DCS with cognitive training resulted in significant improvement of learning in a trained auditory discrimination task, without effects on general cognitive measures (Cain *et al.* 2014). D-serine combined with cognitive training did not induce significant improvement in general cognitive measures (D'Souza *et al.* 2013). The combination of intranasal oxytocin with social skills training significantly enhanced the effects of training on an empathic accuracy task (Davis *et al.* 2014).

In the present study we combined modafinil with cognitive training tasks in patients with schizophrenia. We sought to assess the feasibility of combining a pharmacological compound with a cognitive training program in chronic patients with schizophrenia across two research sites and to test the potential of modafinil to enhance the effects of cognitive training on learning.

We chose modafinil based on evidence from animal and human studies suggesting that modafinil may improve learning and cognition. Acute modafinil administration reverses

deficits in attentional set-shifting in phencyclidine-treated rats (Dawson *et al.* 2012). Acute pre-training modafinil in rodents accelerates the acquisition of simple rules (Béracochéa *et al.* 2003), while repeated doses improve performance in spatial learning, working memory and sustained attention tasks (Béracochéa *et al.* 2002, Tsanov *et al.* 2010, Ward *et al.* 2004). The pro-cognitive effects of modafinil in animal studies are associated with activations in brain regions implicated in learning and cognition, such as prefrontal (PFC) and anterior cingulate cortices (ACC) (Gozzi *et al.* 2012), and with increases of synaptic plasticity in the dentate gyrus of the hippocampus (Tsanov *et al.* 2010).

In healthy, non-sleep deprived individuals, a single dose of modafinil improved sustained attention (Randall *et al.* 2005), working and visual recognition memory, spatial planning and motor impulsivity (Turner *et al.* 2003). Repeated administration of modafinil during a simulated shift-work experiment improved processing speed and divided attention (Hart *et al.* 2006). Modafinil reduces the activation in the ACC and PFC during working memory and attentional control tasks in healthy individuals, which may reflect increased efficiency of prefrontal cognitive information processing (Rasetti *et al.* 2010). A single dose of modafinil improved learning performance in methamphetamine-dependent individuals to levels equivalent to those of healthy controls during an associative learning task; performance improvement was associated with increased activation in brain regions important for learning and cognitive control, such as the ACC, inferior frontal gyrus and bilateral insula (Ghahremani *et al.* 2011).

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). Modafinil modified the function of prefrontal cognitive circuits in patients with schizophrenia: it increased the activation in the ACC during a working memory task (Spence *et al.* 2005) and in the left dorsolateral prefrontal cortex during a cognitive control task (Hunter *et al.* 2006). 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 significant benefits of modafinil on cognition (Lohr *et al.* 2013, Sevy *et al.* 2005). Finally, modafinil has a benign side effect profile and has been associated with minimum

exacerbation of psychotic symptoms in schizophrenia (Scoriels *et al.* 2013), thus providing a reasonable choice for a proof-of-concept trial.

We included six cognitive training tasks to test the potential of modafinil to enhance the effects of cognitive training on learning: a visual learning task that tests processing speed, divided attention and the ability to ignore distracting information (Road Tour task) from PositScienceInsight program (http://www.positscience.com/brain-training-products/insight), an auditory discrimination task that tests processing speed (High or Low task) from PositScienceBrain Fitness Program (http://www.positscience.com/brain-training-products/brain-fitness-program), an implicit visual-auditory learning that tests incidental learning (Language learning task) (Breitenstein and Knecht, 2002), a working memory task (Letter task) (Dahlin *et al.* 2008), a verbal learning and memory task (Verbal List Task) and an executive function task (Shopping Task) from CIRCuiTS, a computerized cognitive remediation package for schizophrenia (http://www.controlled-trials.com/ISRCTN55488371). We chose the study cognitive training tasks to increase the likelihood of enhanced learning following training combined with modafinil. Firstly, performance in these tasks has been shown to improve following training sessions in healthy individuals (Breitenstein and Knecht, 2002, Dahlin *et al.* 2008) and patients with schizophrenia (Fisher *et al.* 2009, Hawkins and Wexler, 1999, Surti *et al.* 2011). Secondly, the cognitive domains trained by these tasks are relevant to CIAS (Dickinson *et al.* 2007) and more importantly are enhanced by modafinil in animal and human studies in healthy individuals and patients with schizophrenia (Dawson *et al.* 2012, Hart *et al.* 2006, Rosenthal and Bryant, 2004, Scoriels *et al.* 2012, Turner *et al.* 2004, Turner *et al.* 2003, Ward *et al.* 2004). Finally, training-induced learning associated with the language learning task used in our study is enhanced by modafinil in healthy individuals (Gilleen *et al.* 2014).

Our primary hypothesis was that participants trained under modafinil would show greater improvement of performance on the trained tasks relative to those trained under placebo. We also examined whether the enhanced learning under modafinil would be sustained after the discontinuation of the combined intervention over a 2-week follow-up period. Our secondary hypothesis was that modafinil-induced enhanced learning would generalise beyond the trained tasks themselves to increased performance on more general cognitive composite scores and proxy measures of everyday functioning.

2. Methods

2.1 Participants

Participants were recruited in two research sites (Institute of Psychiatry, King's College London and University of Manchester). All participants fulfilled the DSM-IV criteria for schizophrenia or schizoaffective disorder and were clinically stable outpatients, treated with stable doses of atypical (other than clozapine) or typical antipsychotics (in the absence of concomitant anticholinergics) for at least 4 weeks prior to the screening visit. Antipsychotic treatment was not changed during the trial. A score of ≤ 4 was required on the Positive and Negative Syndrome Scale (PANSS) (Kay *et al.* 1987). Conceptual Disorganization, Hallucinatory Behaviour and Unusual Thought Content items and on all items of PANSS Negative Subscale. Participants were required to have a raw score ≥6 on the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001) at screening. Sexually active female participants of childbearing potential were included in the study if they were using acceptable methods of contraception for the duration of the trial and for 4 weeks after the discontinuation of modafinil/placebo, and if they had a negative urine pregnancy test at the screening visit. Participants who met DSM-IV criteria for alcohol or substance abuse (other than nicotine) within the last month or DSM-IV criteria for alcohol or substance dependence (other than nicotine) within the last 6 months were excluded from the study, as were participants with a history of significant head trauma, neurological disorder, abnormal findings at physical examination and abnormal ECG at screening visit, uncontrolled hypertension, heart-related conditions and on pharmacological compounds known to affect cognition, such as benzodiazepines and anticholinergics and if taking compounds with known pharmacokinetic interactions with modafinil (e.g. cyclosporine, phenytoin, TCAs). After complete description of the study, participants gave written informed consent. The trial was approved by the West London Research Ethics Committee 2 (REC number 10/H0711/14) and was registered on www.isrctn.org (ISRCTN60687844). All procedures of the study comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Recruitment for the trial began in December 2010 and concluded in September 2012.

2.2. Clinical Trial Design

Participants were enrolled in a double-blind, placebo-controlled study and were randomly assigned to 200mg/day of modafinil or placebo. Stratified randomisation was performed for two preselected factors (gender and smoking status) with known effects on cognition in schizophrenia. Randomisation was implemented via an online system at the

Mental Health & Neuroscience Clinical Trials Unit at the Institute of Psychiatry. To ensure concealment of the randomisation assignment, medication was provided in coded bottles containing identical capsules of active drug or placebo. All participants underwent cognitive training sessions (Please see Supplementary Material for further details on Trial Design).

2.3. Drug treatment

The modafinil dose for the study was 200mg/day, a dose well tolerated in previous clinical studies in patients with schizophrenia (Scoriels *et al.* 2013). The participants received a total of 12 doses of modafinil/placebo, starting at visit 4 through to visit 15. During treatment days, participants were instructed to take the study capsule 2 hours before the scheduled time of their visit at the research sites, as peak plasma concentrations of modafinil are obtained 2-3 hours after oral administration (Wong *et al.* 1999). To ensure high levels of adherence, a reminding telephone call was made to participants on every treatment day 2 hours before the scheduled visit time. Medication adherence was assessed by weekly capsule count and was found to exceed 95%.

2.4. Cognitive training program

Please see Supplementary Material for further details on the cognitive training tasks.

2.5. Cognitive, functional and clinical assessments

Cognitive function was assessed with the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein *et al.* 2008). Alternate forms of tests were used for tests sensitive to practice effects (BVMT-R, HVLT-R and NAB Mazes). Functional capacity was assessed with the University of California San Diego Performance-Based Skills Assessment, brief version (UPSA-B) (Patterson *et al.* 2001). UPSA-B was administered twice, i.e. at the screening and follow-up visits. Trained research assistants performed the neuropsychological assessments after undergoing common training in the administration and scoring of the batteries. Clinical symptoms were assessed with PANSS, which was administered at screening visit, visit 2 and weekly thereafter. Clinically trained researchers conducted PANSS ratings and inter-rater agreement (intraclass correlation coefficient – ICC) was assessed using a standard set of tapes. All PANSS raters had ICC for PANSS total and subscale scores $\geq$.80 and participated in monthly conference calls to maintain inter-rater reliability. All raters were blind to treatment assignment. Vital signs were recorded at screening visit, on a daily basis during treatment and at the follow-up. A side-effect checklist

comprising of 26 modafinil-associated side-effects was rated on a daily basis during treatment and at follow-up.

2.6. Statistical Analyses

The 'CONSORT' flow chart displays the recruitment, representativeness and retention of participants throughout the study (Figure S2). The baseline measures were summarised using descriptive statistics across the randomised groups to ascertain the adequacy of randomisation, with no formal hypothesis testing conducted. We report the amount and patterns of missing outcome data and have assessed the relationship with baseline covariates and randomised group for any systematic differences between the two groups (e.g. evaluate whether more patients leave the modafinil group due to side-effects etc.). The analysis comparing the primary and secondary outcome measures was conducted on 48 participants randomised to either modafinil or placebo, using the intention-to-treat principle (ITT). The primary analysis tested the effects of modafinil/placebo on the performance of the cognitive training tasks using the training data from days 1-10. We utilised mixed effects models with maximum likelihood estimation, including fixed effect terms for day, randomised group (modafinil vs. placebo), the interaction between day and randomised group, and the stratification factors used in the randomisation (gender and smoking status). The 2nd baseline composite score of MCCB, total PANSS and WTAR scores at screening visit were also included as fixed effects in the model. A random intercept was included for each participant. The interaction tests the primary hypothesis that there would be a differential effect between randomised groups on the performance of the cognitive training tasks. Randomised group was effect coded so that the main effect of day could be directly interpreted. We used a nonparametric bootstrap with 500 replications to estimate standard errors for the effects of interest. Conditional on these covariates, under a missing at random (MAR) assumption, the missing data mechanism is ignorable, implying that using maximum likelihood estimation we can include all available outcome measures in the analysis. For the separate analysis of the final cognitive training tasks at follow-up, and the secondary outcomes (MCCB composite score, UPSA-B and PANSS scores), we estimated mixed effects models as before, with a single indicator of time. For the MCCB composite score, we compared separately the measures at 2nd baseline with visit 15 (under the last dose of modafinil/placebo) and follow-up visits respectively, to test for effects at each time point rather than averaged over all time points. All analyses were conducted in Stata version 13.1 using the 'xtmixed' command.

3. Results

3.1. Group characteristics

Please see Figure S2 for a CONSORT flowchart diagram. Of the 21 participants who received modafinil, 19 (90.5%) completed all study visits. Of the 24 who received placebo, 22 (95.6%) completed all study visits. There were no significant screening differences in the participants between recruitment sites or between participants on modafinil and placebo on demographic, clinical, baseline cognitive and functional capacity scores (Table 1).

3.2. Cognitive training tasks

The mixed effects models used to compare the effects of modafinil and placebo on the performance of the trained tasks revealed no significant differences. There was a main effect of time across the combined treatment groups on all cognitive training tasks at the end of the combined intervention and at follow-up, with the exception of High-Low task at follow-up (Table 2). Figure 1 presents the performance on the trained tasks at Day 1, Day 10 and follow-up.

3.3. Neuropsychological, functional and clinical measures

We did not find significant effects of modafinil combined with cognitive training on the MCCB composite and domain scores. There was a main effect of time across the combined treatment groups on the MCCB composite score at the end of the combined intervention and at follow-up (Table 3). Figure 2 shows the effects of treatment on the UPSA-B and PANSS scores. No significant effects of modafinil compared to placebo were found on any of these measures.

3.4. Adverse events

The dose of 200mg/day was very well tolerated. All side effects were of mild severity and no participant was administered any medication for side effect management. One participant was unblinded following increase in blood pressure, which resolved uneventfully (Table S1).

4. Discussion

In this study our first aim was to assess the feasibility of an intervention that combined modafinil with a cognitive training program in patients with schizophrenia across two research sites. During the study, participants were required to be at the research sites every day for ten consecutive weekdays and spend considerable time undergoing the cognitive

training program. Despite the substantial time commitment for study participants, our findings support the feasibility of such combined interventions in schizophrenia in that 84% of the participants enrolled in the trial completed all study visits including follow-up. Our results are in agreement with previous cognitive remediation studies in patients with schizophrenia (Dickinson *et al.* 2010) and also with the study of D'Souza and colleagues (2013), where D-serine was combined with cognitive training in schizophrenia across two research sites (D'Souza *et al.* 2013).

We found significant time effects on the cognitive training tasks across treatment groups and also significant time effects on the MCCB composite score. Beneficial effects of repeated training sessions on the performance of trained tasks have been shown in previous studies in patients with schizophrenia (Davis *et al.* 2014, Dickinson *et al.* 2010, Fisher *et al.* 2009) and our findings on the MCCB composite score are also consistent with previous studies (Davis *et al.* 2014, Horan *et al.* 2011). Thus, although we did not have a control cognitive training intervention in our study, the time effects were in all likelihood induced by cognitive training given the agreement of our findings with previous studies.

Contrary to our primary hypothesis, repeated doses of modafinil did not induce differential enhancement in the performance of the cognitive training tasks compared to placebo. The secondary analysis showed that participants trained under modafinil did not differ significantly from those trained under placebo on the MCCB composite and domain scores and also on the UPSA-B score.

In contrast with our findings, a recent study showed that the combination of DCS or placebo with auditory cognitive training in 36 chronic patients with schizophrenia resulted in significant improvement in a trained auditory discrimination task in the patients trained under DCS. It was suggested that the findings of the study are consistent with animal studies showing that DCS, a partial agonist of the glycine site of the N-methyl-D-aspartate receptor, facilitates memory consolidation, including auditory discrimination memory (Cain *et al.* 2014). Another recent study combined intranasal oxytocin with social skills training in facial emotion recognition, social perception and empathic accuracy in 27 chronic patients with schizophrenia and found that oxytocin significantly enhanced the effects of training on the empathic accuracy task with retention of the effects at 1 month follow-up. It was suggested that oxytocin may have enhanced learning by increasing the salience of social information (Davis *et al.* 2014). However, it remains unclear why oxytocin enhanced only empathic accuracy and not the other social skills that were trained in the study.

Despite evidence from animal and human studies that the domains trained by the tasks in our study are enhanced by modafinil, we did not find any significant effects on learning. Several explanations are possible.

Several explanations are possible. Limited statistical power is a common issue in both drug and cognitive remediation trials in schizophrenia. Since no other combination studies were available in schizophrenia, we based the estimate of the group size on combination studies in healthy individuals and other clinical populations. Our group size was larger than the samples of two previous studies, which used the original version of the New Language learning task we included in our cognitive training program. In these studies, 40 healthy individuals were trained under levodopa/placebo (Knecht *et al.* 2004) and amphetamine/placebo (Breitenstein *et al.* 2004) for five days. Both levodopa and amphetamine significantly increased novel word learning compared to placebo with medium effect sizes (Cohen's d=0.69 and Cohen's d=0.66 respectively). Our group was also larger than the groups of the D-cycloserine and behavioural therapy combination studies for anxiety disorders included in the relevant meta-analysis (Norberg *et al.* 2008), which ranged from 23 to 31 participants [with the exception of one study that included 56 participants (Guastella *et al.* 2008)]; the size of treatment effect in these studies was in the medium range (Cohen's d=0.60). Thus, while our study should have had sufficient power to detect an effect of this magnitude, it would have missed a smaller effect. However, inspection of our data showed little evidence of any effect even at trend level; it seems therefore unlikely that the lack of significant findings could be accorded only to a limited sample size.

Participant age and duration of illness could have played a role in the absence of effects of modafinil on learning. The participants of our study were in their mid-to-late thirties and chronically ill. The effects of age and illness chronicity have been suggested to account in part negative results of cognitive-enhancing drugs in schizophrenia so far and it has been suggested that younger patients earlier in the course of the illness may have greater potential for cognitive improvement (Keefe *et al.* 2011). Participant age is also associated with lower cognitive effects in cognitive remediation studies (Wykes *et al.* 2009). In the absence of a repeated-dose randomised trial in first-episode patients with schizophrenia, we cannot rule out that the combination of cognitive training with modafinil might have worked in such a population.

Another factor that could have contributed to the lack of modafinil's effects on learning is the duration of the combined intervention. We administered a total of 10 training sessions in combination with modafinil/placebo on 10 consecutive weekdays across 2 weeks. In a study

in healthy volunteers implemented in our laboratory modafinil augmented the training-induced effects on learning in the language learning task also used in the present study, after 5 training sessions (Gilleen *et al.* 2014). Additionally, the duration of the combined intervention in our study was similar to the duration in the study of Davies and colleagues (2014) (Davis *et al.* 2014), where oxytocin/placebo was combined with social skills training, in a total of 12 training sessions across 6 weeks and resulted in enhancement of the training-induced effects of learning on an empathic accuracy task. Conversely, in the study of Cain and colleagues (2014) (Cain *et al.* 2014), the number of training sessions combined with DCS ranged between 24 and 40 across 8 weeks and resulted in enhancement of learning on an auditory discrimination task. It seems therefore that the optimal duration of such combined interventions for enhancement of learning in schizophrenia warrants further investigation.

In our study we administered multiple doses of modafinil. Evidence for the effects of modafinil on cognition in schizophrenia so far, has shown significant effects in two single dose studies (Scoriels *et al.* 2012, Turner *et al.* 2004) and only in one repeated administration study (Rosenthal and Bryant, 2004), while all other repeated administration studies have failed to demonstrate significant cognitive effects (Scoriels *et al.* 2013). A possible explanation for the difference between single- and multiple-dose effects could be the development of tolerance to any beneficial short-term cognitive effects of modafinil in patients with schizophrenia. Alternatively, the lack of improvement in both the cognitive training tasks and the cognitive measures with modafinil may be related to the dose used in our study (200mg/day). Studies in rodents suggest that pre-training administration of modafinil improves performance in working memory, sustained attention and response inhibition tests in a dose-dependent manner with the higher doses being the most efficacious (Eagle *et al.* 2007, Morgan *et al.* 2007). Similarly, the effects of modafinil on stop-signal reaction time measures in healthy individuals are dose-dependent (Turner *et al.* 2003). The modafinil studies in schizophrenia have used doses ranging between 100 and 250mg/day (Scoriels *et al.* 2013) and to the best of our knowledge no published studies so far have investigated dose-dependency of modafinil's cognitive effects in schizophrenia. Therefore, a dose-response pattern on the effects of modafinil on learning and cognition in schizophrenia cannot be excluded.

The lack of cognitive effects of the combination of modafinil and cognitive training in our study is in agreement with the findings of a recent study, where 104 patients with schizophrenia were trained under D-serine or placebo for 12 weeks and were followed-up for another 24 weeks. One the main reasons that was suggested to account for the lack of effects

is that the dose of D-serine used in that study (30mg/Kg) was too low to exert cognitive effects (D'Souza *et al.* 2013). Furthermore, the combination of DCS with computerised cognitive training in patients with schizophrenia did not enhance cognition, as measured by MCCB (Cain *et al.* 2014). Similar to ours, the participants of both studies above were in their mid-to-late thirties and chronically ill, which could have also contributed to the lack of cognitive effects.

Overall, the results of our study indicate that interventions combining a pharmacological compound with cognitive training in patients with schizophrenia are feasible. Repeated doses of modafinil did not augment training-induced learning associated with the training tasks in chronic patients with schizophrenia and did not improve general cognitive performance. The interventions that combine training with pharmacological compounds for learning and cognitive impairment have just started to be explored in schizophrenia and issues such as choice of drug and optimal dose, chronicity of illness, cognitive domains to be trained and cognitive outcome measures require further investigation in future studies.

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Conflict of Interest

Prof. Kapur has received grant support from AstraZeneca, Bristol-Myers Squibb and GlaxoSmthKlline and has served as consultant, scientific advisor and had speaking engagements for AstraZeneca, Bioline, Bristol Meyers Squibb, Eli Lilly, Janssen (Johnson & Johnson), Lundbeck, NeuroSearch, Otsuka, Pfizer, Roche, Servier, Solvay and Wyeth. Prof. Lewis has served as scientific advisor and has speaking engagements for AstraZeneca, Lilly and Johnson & Johnson. Dr. Pandina is a full-time employee and a stockholder of Johnson & Johnson. Drs. Michalopoulou, Drake, Reichenberg, Emsley, Kalpakidou, Lees, Gilleen, Applegate, Mrs Bobin and Prof. Wykes declare that they have no conflicts of interest in relation to the subject of this study.

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Figure(s)
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Figure 1. Cognitive training task performance at Day 1, Day 10 and follow-up

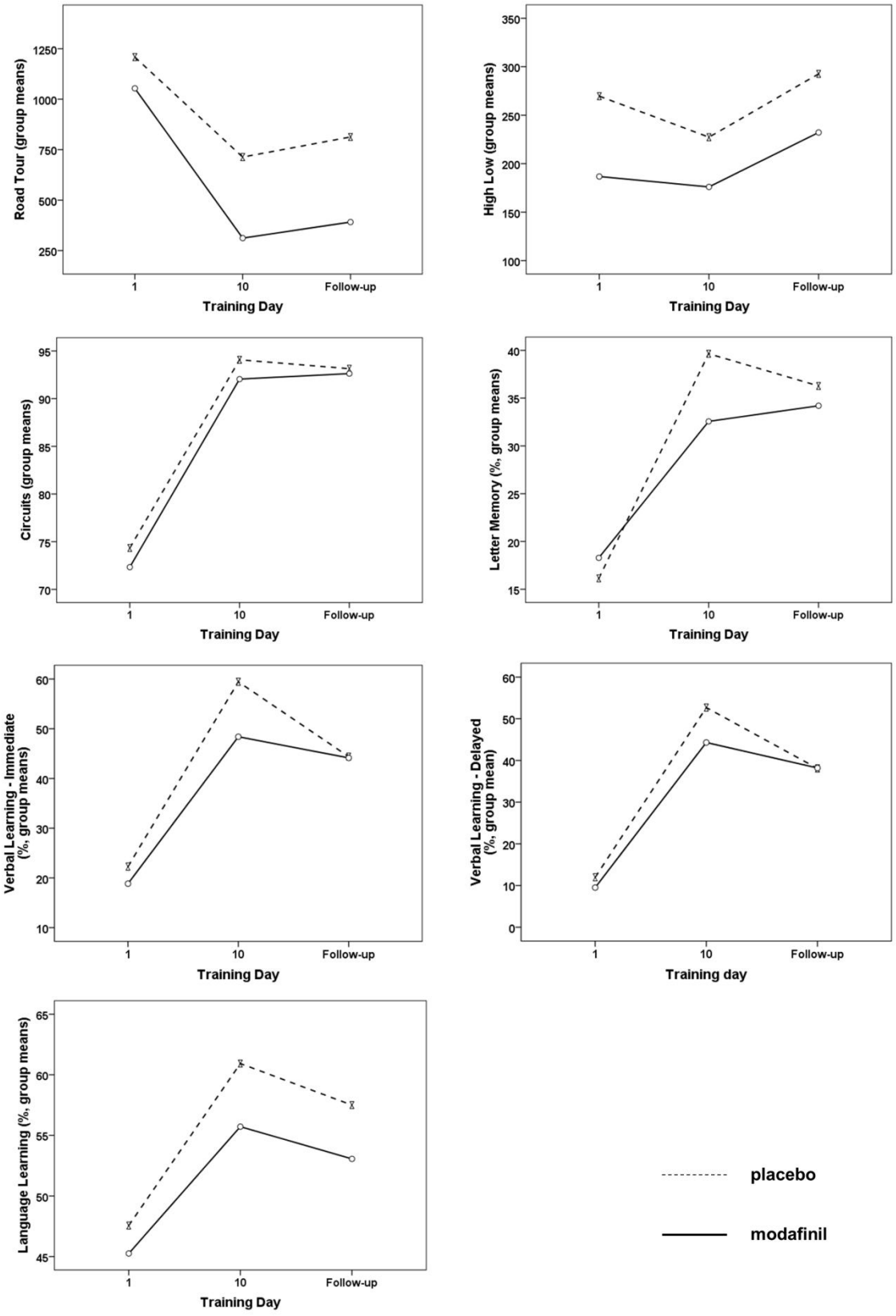
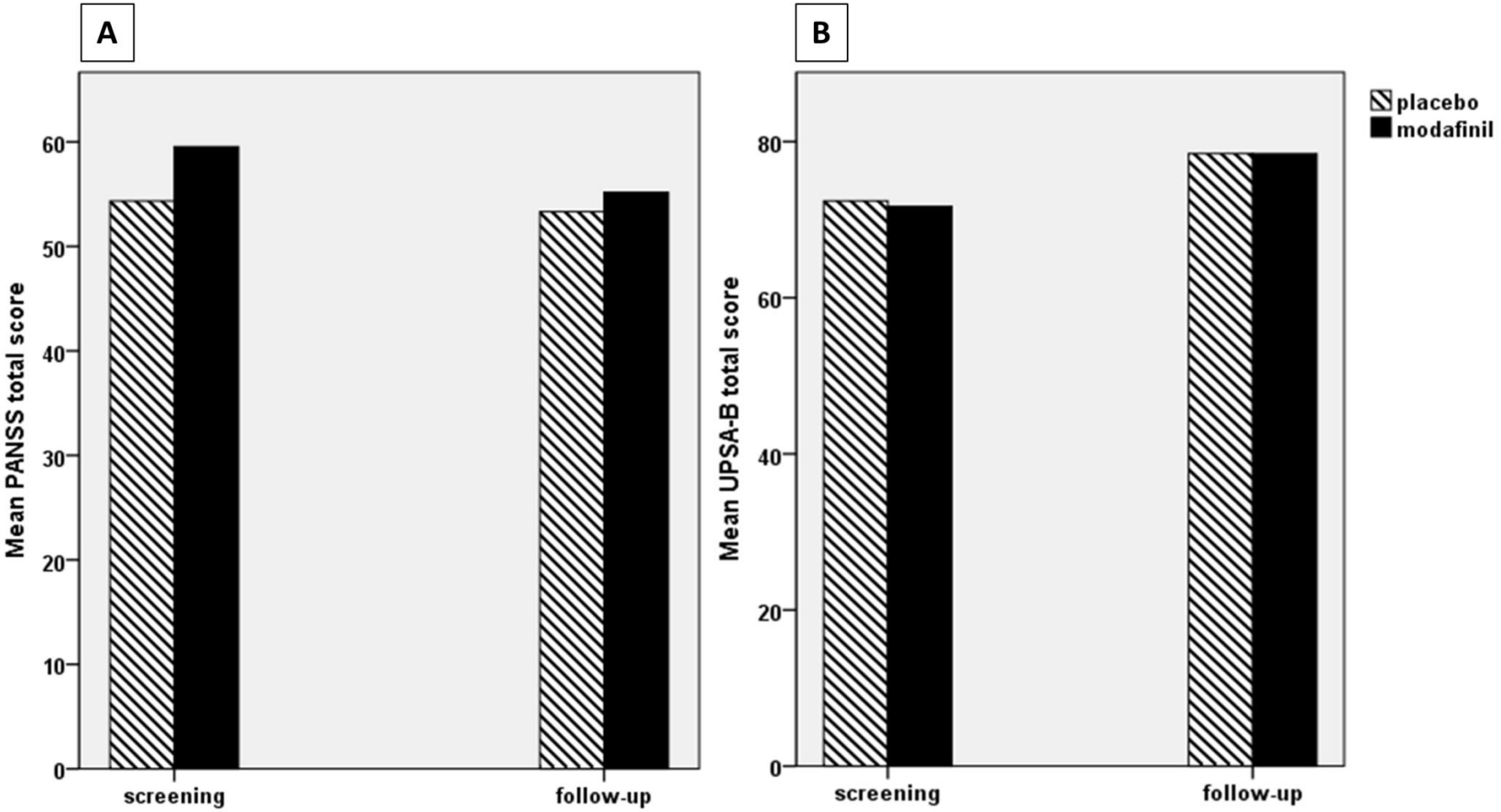


Figure 2. PANSS and UPSA–B scores



The effect of treatment group was not significant at follow-up for: A) PANSS (adjusted mean difference= 0.6, z= 0.25, p= 0.805) and B) UPSA-B (adjusted mean difference= 1.923, z= 0.70, p= 0.486) total scores

Table 1. Demographic and clinical characteristics

Variable *	Placebo (n = 24)	Modafinil (n = 24)
Males/Females	17/7	18/6
Age (years)	35.4 (9.9)	37.2 (9.6)
Ethnicity		
▪ Caucasian	7 (29.2%)	8 (33.3%)
▪ African-Caribbean	16 (66.6%)	12 (50.0%)
▪ Asian	0 (0%)	3 (12.5%)
▪ Other	1 (4.2%)	1 (4.2%)
Years of education [a]	12.7 (3.1)	12.3 (1.9%)
Currently smoking (Yes/ No)	14/10	17/7
Duration of illness (years)	12.1 (8.7)	12.1 (7.1)
Age at illness onset (years)	23.3 (7.4)	25 (7.2)
WTAR Raw score	33.9 (10.7)	30 (9.3)
UPSA-B at screening visit/follow-up [b]	72.4 (14.2)/78.5 (11.71)	71.7 (9.9)/78.4 (14.5)
PANSS scores at screening visit/follow-up [b]		
▪ Positive	12.3 (4.5)/12.5 (4.7)	13.7 (4.6)/12.1 (3.3)
▪ Negative	15 (4.5)/14.6 (5.2	16.1 (4.4)/16.1 (4.5)
▪ General	27 (5.3)/26.2 (5.6)	29.8 (8)/27 (5.8)
▪ Total	54.3 (11.8)/53.3 (13.3)	59.5 (14)/55.2 (11.9)
Chlorpromazine equivalents	254.2 (195.3)	275 (138.7)
Atypical /Typical antipsychotics	18/4	21/2
Concomitant psychiatric medications		
▪ SSRIs	2	5
▪ NaSSAs (Mirtazapine)	1	2
▪ SNRIs (Venlafaxine)	1	0
▪ NRIs (Reboxetine)	0	1
▪ Mood stabilizers	3	1

*Mean and standard deviation (SD) are presented, unless otherwise stated [a] For Modafinil, n = 1 missing data [b] For Placebo, n = 2 missing data, for Modafinil, n = 5 missing data

Table 2. Cognitive training data for study participants

Cognitive Training task[+]		Treatment arm assignment		Time Effect			Treatment Effect[a]		
	Day	Placebo (n= 24)	Modafinil (n= 24)	Effect	Z	p-value	Effect	Z	p-value
Road tour	Day 1	1128.1 (1068.8)	1220.1 (1171.3)						
(time to complete in ms)	Day 10	610.6 (1038.1)	398.8 (391.8)	-62.3	-5.8	**<0.001**	-19.6	-1.8	0.068
	Follow-up	695.3 (1035.4)	495.4 (609.5)	-571.6	-4.5	**<0.001**	-198.2	-1.6	0.107
Hi/Low	Day 1	247.4 (287.7)	277.2 (324.8)						
(time to complete in ms)	Day 10	242.4 (305.1)	203.8 (274.0)	-7.5	-2.7	**0.008**	-1.5	-0.5	0.605
	Follow-up	282.6 (321.4)	202.8 (295.9)	-9.4	-0.2	0.875	-53.8	-0.9	0.347
Circuits	Day 1	74.7 (25.3)	73.3 (22.6)						
(number)*	Day 10	93.9 (6.7)	88.2 (22.1)	2.1	6.0	**<0.001**	-0.3	-0.9	0.361
	Follow-up	91.8 (9.9)	92.6 (7.9)	18.3	4.4	**<0.001**	1.1	0.3	0.787
Letter memory	Day 1	14.7 (15.6)	17.5 (16.8)						
(% correct responses)	Day 10	36.6 (30.5)	32.6 (25.2)	1.6	5.2	**<0.001**	-0.2	-0.5	0.600
	Follow-up	35.2 (29.0)	34.2 (28.1)	17.8	4.1	**<0.001**	-1.7	-0.4	0.693
Verbal learning – Immediate	Day 1	21.3 (8.8)	19.2 (9.3)						
(% correct responses)	Day 10	59.5 (23.7)	48.4 (27.8)	3.5	9.7	**<0.001**	-0.3	-0.9	0.387
	Follow-up	44.3 (22.9)	44.1 (22.5)	23.5	7.5	**<0.001**	1.1	0.4	0.725
Verbal learning – Delayed	Day 1	10.9 (8.5)	10.0 (6.2)						
(% correct responses)	Day 10	52.7 (24.8)	44.3 (28.1)	4.2	10.4	**<0.001**	-0.2	-0.6	0.558
	Follow-up	37.2 (24.7)	38.2 (25.4)	26.8	7.1	**<0.001**	1.0	0.3	0.774
Language learning	Day 1	47.6 (4.3)	43.8 (7.1)						
(% correct responses)	Day 10	60.9 (12.3)	54.8 (7.2)	1.2	6.5	**<0.001**	-0.2	-1.1	0.290
	Follow-up	57.8 (11.4)	52.8 (4.8)	9.4	5.5	**<0.001**	-0.6	1.7	0.702

[+] Mean and standard deviation (SD) are presented *The score (number) for the Circuits represents response accuracy and response time [a] Interaction between randomised group and day to test the primary hypothesis that there would be a differential effect between randomised groups on the performance of the cognitive training tasks

Table 3. MCCB Composite and cognitive domain T-scores

Cognitive domain[+]	Session	Treatment arm assignment		Linear Mixed Model Results					
		Placebo (n= 24)[a]	Modafinil (n= 24)[b]	Treatment effect	Z	p-value	Time effect	Z	p-value
MCCB Composite	Baseline	30.6 (12.1)	26.6 (12.7)						
	End of combined intervention	32.8 (15.1)	29.7 (15.3)	-0.2	-0.3	0.790	2.7	3.3	**<0.001**
	Follow-up	34.1 (14.7)	30.6 (15.1)	-0.6	-0.7	0.481	3.9	4.6	**<0.001**
Speed of processing	Baseline	34.7 (13.4)	28.4 (12.3)						
	End of combined intervention	36.0 (16.6)	32.6 (12.1)	0.9	0.9	0.393	3.0	2.8	**0.005**
	Follow-up	37.9 (14.1)	34.8 (14.9)	1.2	1.1	0.281	4.9	1.2	**<0.001**
Attention/Vigilance	Baseline	38.0 (11.7)	34.6 (11.9)						
	End of combined intervention	38.7 (13.9)	36.5 (13.5)	-0.3	-0.3	0.751	1.5	1.6	0.101
	Follow-up	38.1 (14.6)	36.1 (13.6)	-0.3	-0.2	0.820	1.1	1.0	0.299
Working memory	Baseline	39.7 (10.2)	36.6 (12.3)						
	End of combined intervention	42.3 (12.8)	38.5 (13.3)	-1.0	-0.9	0.348	2.1	2.0	**0.045**
	Follow-up	43.0 (12.9)	40.5 (13.0)	-0.6	-1.0	0.319	3.7	6.1	**<0.001**
Verbal learning	Baseline	38.9 (9.6)	34.4 (7.1)						
	End of combined intervention	37.9 (11.1)	34.7 (8.6)	0.4	0.4	0.702	-0.4	-0.3	0.741
	Follow-up	37.6 (8.3)	35.8 (7.8)	1.2	1.0	0.309	0.0	0.0	0.973
Visual learning	Baseline	36.1 (14.6)	36.8 (14.9)						
	End of combined intervention	39.4 (15.3)	37.6 (13.9)	-1.4	-1.0	0.331	2.5	1.8	0.077
	Follow-up	43.1 (16.0)	38.2 (13.9)	-3.2	-1.8	0.074	4.5	2.7	0.007
Reasoning and problem solving	Baseline	39.1 (9.9)	41.5 (8.6)						
	End of combined intervention	41.9 (10.6)	41.7 (10.4)	-1.4	-1.3	0.192	1.7	1.7	0.091
	Follow-up	42.9 (10.5)	41.5 (10.4)	-2.3	-1.8	0.080	2.3	1.8	0.077
Social cognition	Baseline	40.0 (8.9)	37.2 (10.8)						
	End of combined intervention	39.7 (8.3)	41.2 (12.8)	1.8	1.5	0.123	1.3	1.2	0.265
	Follow-up	39.2 (10.0)	39.5 (9.6)	1.1	0.9	0.371	0.4	0.4	0.720

[+] Mean and standard deviation (SD) are presented [a] For Placebo, n= 2 missing data for all cognitive domains during all sessions [b] For Modafinil, Baseline, n= 3 missing data for all cognitive domains; End of combined intervention, n= 5 missing data for all cognitive domains; Follow-up, n= 6 missing data for MCCB Composite, Speed of processing, Attention/Vigilance and Reasoning and problem solving domains, and n= 5 missing data for Working memory, Verbal learning, Visual learning and Social cognition domains

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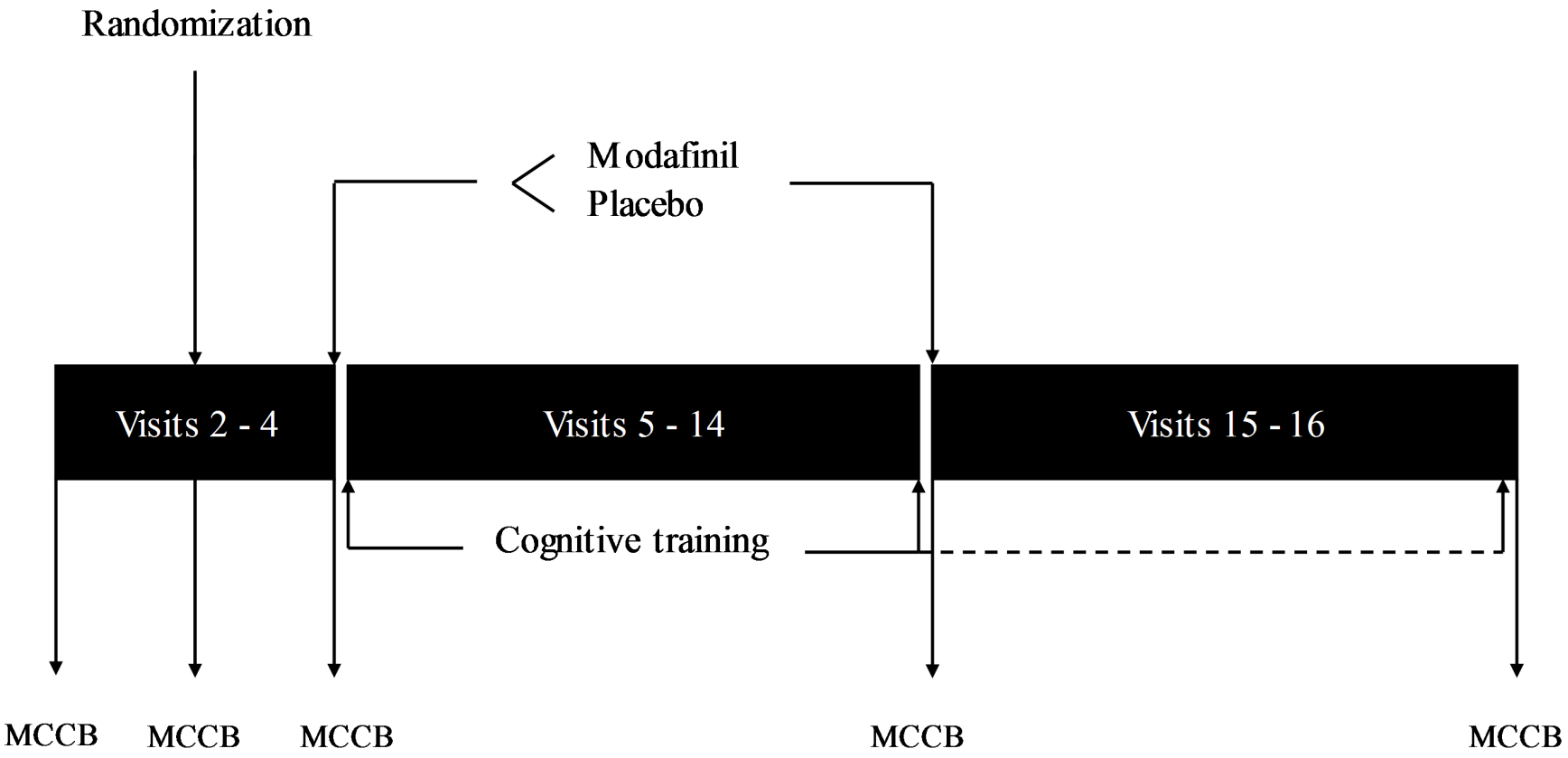
Figure S1. Study Design



Study Design Description

Participants received a total of 16 visits (Figure S1). Following the screening visit (visit 1), participants underwent neuropsychological assessments during the two subsequent visits (visits 2 and 3), which served as a dual baseline to minimise practice effects. Following randomisation, the first dose of modafinil/placebo was given during visit 4 and the participants underwent neuropsychological assessment to investigate the effects of a single dose of modafinil on cognitive performance (The cognitive effects of the single dose of modafinil are not reported in this article). The 11 subsequent visits (visits 5 – 15) were on consecutive weekdays. Participants underwent the study intervention, i.e. the combination of modafinil/placebo and cognitive training program for 10 visits (visits 5-14). During visit 15, neuropsychological assessments only were performed under the last dose of modafinil/placebo. The last study visit (visit 16) occurred two weeks after visit 15 and participants underwent the cognitive training program and neuropsychological assessments. Participants did not receive cognitive training sessions or modafinil/placebo between visits 15 and 16. Participants received financial compensation for their time in the study.

Cognitive training Tasks

Road Tour task: A computer-based task, which is one of the exercises in Posit Science's InSight visual training software (http://www.positscience.com/brain-training-products/insight). Briefly, participants were asked to match a vehicle that appeared for a very short period of time in the centre of the screen with a vehicle that appeared subsequently and also to show the location where a peripheral target appeared. Depending on the performance of the participant, the vehicles to be matched become more similar and distractors for the peripheral target are added. The outcome measure used was time to complete the task in milliseconds and the duration of training was 10 minutes every training day.

High-Low task: A computer-based explicit auditory task, which is one of the exercises of Posit Science's Brain Fitness Program, which is detailed in Fisher and colleagues (2009). Briefly, participants were asked to discriminate between a high and a low frequency sound. Depending on the performance of the participant, the sounds to be discriminated sounded closer together, faster and got subtly different in pitch. The outcome measure used was time to complete the task in milliseconds and the duration of training was 10 minutes every training day.

Circuits: This task is a part of the Computerised Interactive Remediation of Cognition – Training for Schizophrenia - CIRCuiTS), a computerized cognitive remediation therapy programme, that has been developed by a multidisciplinary team (academic, service users and technical software at SPIKA Ltd) at the Institute of Psychiatry**.** Briefly, participants were presented with a shopping list at a supermarket and were asked to locate and select the items. The task difficulty level was moderated based on participant's prior performance. The outcome measure was an automatically calculated score representing response accuracy and response time and the duration of training was 10 minutes every training day.

Letter memory Task: A working memory task, detailed in Dahlin and colleagues 2008. Briefly, the letters A, B, C and D were serially presented in lists of varied length. There were 3 levels of task difficulty depending on the list length: Easy: 4–7 letters, medium: 6–11 letters and hard: 5–15 letters. The task begun with the presentation of 5 trials of "easy" lists. Participants were asked to recall the last four presented letters when the presentation of the list ended. Four correct responses in 5 trials moved the participant to the next difficulty level. The outcome measure was the percentage of correct responses and the duration of training was 10 minutes every training day.

Verbal Learning task: A verbal learning and memory task, which consisted 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 were asked to recall as many words as possible. There was also a delayed recall phase at the end of each training day. The outcome measure was the percentage of correct responses and the duration of training was 6-8 minutes every training day.

Language Learning Task: An implicit auditory-visual computer-based new-language learning task developed by Breitenstein and Knecht, where a detailed description of the task can be found. In summary, 50 pseudowords were paired with an object drawing in a pseudo-randomized manner. Participants indicated by button press whether they thought a particular coupling to be correct or incorrect. The underlying learning principle is higher co-occurrence of certain couplings (i.e. the correct couplings) as compared with other couplings (i.e. the incorrect couplings). The outcome measure was the percentage of correct responses (for both correct and incorrect couplings) and the duration of training was 10 minutes every training day.

Figure S2. Study CONSORT flow chart

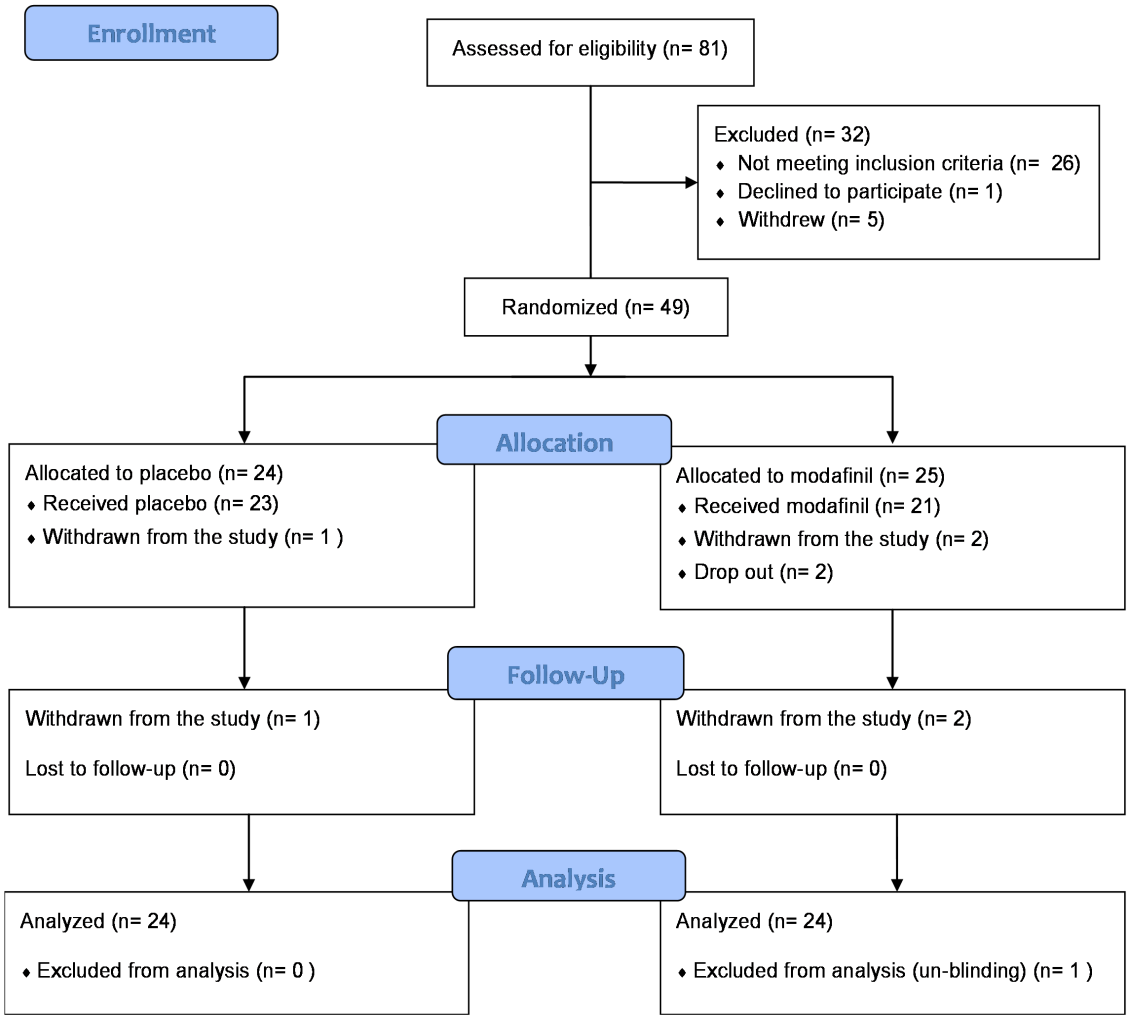


Table S1. Adverse Events

Adverse Event	Modafinil number (%)	Placebo number (%)
Headache	9 (18.37)	4 (8.16)
Dry mouth	8 (16.33)	3 (6.12)
Dizziness	6 (12.24)	4 (8.16)
Insomnia	5 (10.20)	4 (8.16)
Nervousness	4 (8.16)	0 (0.00)
Anxiety	4 (8.16)	2 (4.08)
Flu syndrome	4 (8.16)	1 (2.04)
Nausea	3 (6.12)	4 (8.16)
Rhinitis	3 (6.12)	4 (8.16)
Back pain	2 (4.08)	1 (2.04)
Diarrhoea	2 (4.08)	1 (2.04)
Dyspepsia	2 (4.08)	1 (2.04)
Pharyngitis	2 (4.08)	1 (2.04)
Anorexia	1 (2.04)	0 (0.00)
Chest pain	1 (2.04)	1 (2.04)
Hypertension	1 (2.04)	0 (0.00)
Tachycardia	0 (0.00)	1 (2.04)
Palpitations	0 (0.00)	1 (2.04)
Constipation	0 (0.00)	1 (2.04)