Modafinil Modulates Resting-State Functional Network Connectivity and Cognitive Control in Alcohol-Dependent Patients

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Background: Chronic alcohol abuse is associated with deficits in cognitive control functions. Cognitive control is likely to be mediated through the interaction between intrinsic large-scale brain networks involved in externally oriented executive functioning and internally focused thought processing. Improving the interaction between these functional brain networks could be an important target for treatment. Therefore, the current study aimed to investigate the effects of the cognitive enhancer modafinil on within-network and between-network resting-state functional connectivity and cognitive control functions in alcohol-dependent patients.

Methods: In a double-blind, placebo-controlled cross-over design, resting-state functional magnetic resonance imaging and a Stroop task were employed in alcohol-dependent patients ($n = 15$) and healthy control subjects ($n = 16$). Within-network and between-network functional connectivity was calculated using a combination of independent component analysis and functional network connectivity analysis.

Results: Modafinil significantly increased the negative coupling between executive networks and the default mode network, which was associated with modafinil-induced improvement in cognitive control in alcohol-dependent patients.

Conclusions: These findings demonstrate that modafinil at least partly exerts its effects by targeting intrinsic functional relationships between large-scale brain systems underlying cognitive control. The current study therefore provides a neurobiological rationale for implementing modafinil as an adjunct in the treatment of alcohol dependence, although clinical studies are needed to substantiate this promise.

Key Words: Alcohol dependence, cognitive control, functional network connectivity, independent component analysis, modafinil, resting-state fMRI

Chronic alcohol and drug abuse has been associated with cognitive impairments, including deficits in cognitive control (1). Cognitive control can be defined as flexible, goal-directed behavior that requires a mechanism for guidance to allow for appropriate actions in the face of contextually relevant information (2). Aspects of cognitive control include the ability to resolve conflict-inducing situations and to inhibit prepotent responses and can be measured with neurocognitive tasks, including the Stroop task (3). These processes are especially relevant in the context of addiction, since inhibition of a prepotent response (e.g., compulsive drug use), especially when confronted with drug-related cues (contextual relevant information), is critical for abstaining from drug use. Indeed, diminished cognitive control has been found to predict treatment retention and relapse into drug use (4,5). Enhancing cognitive control functions is therefore an important target for the treatment of alcohol dependence.

A promising compound for reinforcing cognitive control is modafinil, a wakefulness-promoting drug approved for the treatment of narcolepsy and widely used as a cognitive enhancer (6). Modafinil has been shown to improve cognitive control in patients with methamphetamine dependence (7) and pathological gambling (8). However, there is only limited information on the mechanisms by which modafinil improves cognitive control in patients with addictive behaviors in terms of underlying neural substrates. This is important to know because it would increase not only our insight into neurobiological mechanisms of distorted cognitive control but also our understanding of the treatment of psychiatric conditions characterized by such deficits. Therefore, the current study aimed to investigate the effects of a single dose of modafinil on neural substrates related to cognitive control in alcohol-dependent patients and healthy control subjects.

Previous functional magnetic resonance imaging (fMRI) studies have indicated that adequate cognitive control relies on intact functioning of executive brain networks comprising brain regions such as the dorsal anterior cingulate cortex (dACC), dorsolateral prefrontal cortex (DLPFC), and parietal cortex (9,10). The dACC, together with the anterior insula, is part of a large-scale distributed network that is activated in tasks of cognitive control (2) but also in response to pain, uncertainty, and other homeostatic challenges (11,12), which suggest a general role of this functional network in salience processing. Therefore, this circuit is often referred to as the brain's salience network (SN) (13). In addition, lateral frontal and parietal regions are often found to be co-activated during cognitive control tasks (14) and together form the so-called central executive network (CEN) (15).

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Received Sep 13, 2012; revised Nov 26, 2012; accepted Dec 29, 2012.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2012.12.025

In addition to these networks, which are activated during cognitive control tasks, a set of interconnected brain regions, including ventromedial prefrontal cortex, posterior cingulate cortex (PCC), and inferior parietal lobe, is suppressed during tasks that demand externalized attention (16). This network is referred to as the default mode network (DMN) and is usually activated by cognitive processes that are internally focused, such as self-reference and recollecting one's past or imagining one's future (16). Recent studies have indicated that not just the activation or deactivation of these functional networks but especially the interaction between the task-positive networks and the DMN is crucial for performance of cognitive tasks (17–19). Switching between externally and internally oriented cognition is thought to be reflected by a competitive relationship (anticorrelation) between the DMN and both the SN and CEN (20).

Such anticorrelations between these networks are not only present during the performance of cognitive tasks but also during rest in the absence of sensory input (20), suggesting that the brain may be intrinsically organized to support competitive relationships between networks involved in externally and internally oriented cognition. Moreover, spontaneous fluctuation in these resting-state functional networks and the strength of the anticorrelation between the DMN and the SN and CEN predict individual performance variability in several cognitive domains (21,22), including cognitive control (13,17). The relevance of studying resting-state functional networks is that it allows us to examine the overall functional organization of the brain and its adaptive potential when state-dependent shifts from baseline levels are needed as a response to a changing environment or changing cognitive demands.

Previous fMRI studies in healthy individuals (23) and patients with schizophrenia (24,25) and methamphetamine dependence (26) have indicated that modafinil enhances efficiency of prefrontal and dACC processing during the performance of cognitive tasks and leads to task-induced deactivation of the DMN. However, the effects of modafinil on the intrinsic properties of brain functioning in the form of resting-state functional networks have not been investigated. Therefore, the current study examined the effects of modafinil on within-network and between-network functional coupling of the DMN and the SN and CEN using resting-state fMRI. In resting-state fMRI literature, the SN and CEN are also often referred to as task-positive networks, although no actual task is performed; therefore, the term task-positive networks is used interchangeably with the terms SN and CEN throughout this article. In addition, we examined whether within-network and between-network connectivity changes were associated with modafinil-induced changes in cognitive control measured by a Stroop task. We hypothesized that modafinil would enhance within-network connectivity and modulate between-network connectivity, reflected in an increased competitive relationship (anticorrelation) between the DMN and task-positive networks, and that this would translate into modafinil-induced improvements in cognitive control.

Methods and Materials

Subjects

The present study was part of a larger fMRI study investigating the effects of modafinil on neural correlates of cognitive control in alcohol-dependent patients. In the current report, only subjects with complete resting-state fMRI data are described. For the larger study, 20 male subjects meeting DSM-IV (27) criteria for alcohol dependence (AD) were recruited from regional addiction treatment centers. In addition, 18 healthy control subjects (HC), matched on sex, education, and age, were included. Exclusion criteria can be found in the Methods in Supplement 1. Five AD and two HC subjects were excluded from the current analyses (Methods in Supplement 1). The remaining data from 31 participants (15 AD, 16 HC) were used in statistical analyses. All subjects gave written informed consent to participate in this study, which was approved by the Medical Ethical Committee of the Academic Medical Center of the University of Amsterdam.

Design

This study had a randomized, double-blind, placebo-controlled, within-subjects crossover design. Each subject participated in two sessions separated by 1 week. In the first session, subjects either received tablets of modafinil (total 200 mg) or placebo tablets. In the second session, subjects were crossed over to receive the opposite medication. Six AD subjects and eight HC subjects received modafinil in the first session and placebo in the second session. For details on the randomization procedure, see Methods in Supplement 1. Medication was administered 2 hours before fMRI, because peak plasma levels occur at 2 to 4 hours after a single dose (28).

Clinical Assessments

All subjects were screened for the presence of Axis I psychiatric disorders using the Mini-International Neuropsychiatric Interview (29). General intelligence (IQ) was assessed using the National Adult Reading Test (30). Alcohol and drug consumption during the preceding 6 months was quantified using the Time Line Follow Back method (31). In addition, the Alcohol Use Disorder Identification Test (AUDIT) (32) was used to identify harmful patterns of alcohol consumption.

Stroop Task

Subjects performed a classic Stroop color-word paradigm (3) outside the magnetic resonance imaging (MRI) scanner (see Methods in Supplement 1 for details). Subjects were presented with color words printed in red, blue, yellow, or green fonts, resulting in either congruent (e.g., word red printed in red font) or incongruent stimuli (e.g., word red printed in blue font). Subjects were asked to identify the font color as quickly and accurately as possible, using a button press, while suppressing automatic word reading. The difference in mean reaction time between incongruent and congruent stimuli, referred to as the interference score, was calculated to obtain a measure of cognitive control. Smaller interference scores indicate greater cognitive control.

Imaging Protocol

Magnetic resonance imaging data were obtained using a 3.0T Intera MRI scanner (Philips Healthcare, Best, The Netherlands) equipped with a SENSE eight-channel receiver head coil. For the resting-state scan, a gradient-echo echo-planar imaging sequence sensitive to blood oxygen level–dependent contrast (repetition time/echo time = 2300 msec/25 msec, matrix size 64 × 64, voxel size 2.29 × 2.29 × 3 mm, 38 slices, no gap) was used to acquire 200 images. During the resting-state scan, subjects were instructed to relax, keep their eyes closed, and to stay awake. After the resting-state scan, subjects were asked whether they managed to stay awake. Three-dimensional T1-weighted images were collected using a gradient-echo sequence (repetition time = 9 msec; echo time = 3.5 msec; 170 slices; voxel

size 1 × 1 × 1 mm; matrix size 256 × 256) for anatomical reference with the echo-planar imaging data.

Data Analysis

Behavioral Data. Demographic and Stroop task performance data were analyzed using the Statistical Package for the Social Sciences (SPSS 16, Chicago, Illinois). Stroop interference scores were not normally distributed and were therefore log-transformed. Differences in baseline characteristics between groups were analyzed using independent *t* tests. A repeated measures analysis of covariance was conducted to assess Stroop task performance with treatment (modafinil versus placebo) modeled as a within-subject factor and group (AD vs. HC) as a between-subjects factor, including session order as a covariate. The significance level was set to $p < .05$.

Imaging Data. Imaging data were preprocessed using Statistical Parametric Mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London, United Kingdom). Functional images of each individual subject were realigned and unwarped to correct for motion. The images were subsequently co-registered with the structural MRI image and then segmented for normalization to a Montreal Neurological Institute template. Finally, images were smoothed using an 8 mm full-width at half maximum Gaussian kernel.

The GIFT group ICA toolbox (33) (http://icatb.sourceforge.net) using the infomax algorithm was performed on preprocessed blood oxygen level–dependent data to identify 23 spatially independent and temporally coherent resting-state components. For details, see Methods in Supplement 1. The DMN, SN, and CEN components were visually identified through comparison with previous literature, based on their spatial configurations and the power spectral density of the associated time courses (34,35).

One-sample *t* tests, with a threshold of $p < .05$ family-wise error whole-brain corrected, were conducted on each network across groups and across sessions to visualize the networks and to create a mask for each network containing the brain regions that significantly contributed to the network, which served as a region of interest. A global connectivity index derived from the mean value of the region of interest (MarsBaR toolbox [36]) corresponding to the significant clusters of the connectivity maps was determined for each subject and each network. This index represents the value of the magnitude of the correlation between all the regions composing the network (within-network connectivity).

Functional coupling between the DMN and the task-positive networks (between-network connectivity) was calculated using the FNC toolbox (37) (http://icatb.sourceforge.net), which uses constrained lagged correlation between components. Maximal lagged correlation (−5 to +5 seconds) was examined between all pairwise combinations of components of interest, calculated for each subject. The within-network global connectivity values and pairwise correlation coefficients between networks were extracted to SPSS. The pairwise correlation coefficients were transformed into Fisher's *Z* values. Repeated measures analyses of covariance were conducted on within-network and between-network connectivity strength with treatment modeled as a within-subject factor and group as a between-subjects factor, including session order as a covariate. In addition, whole-brain voxel-wise statistical analyses were performed on the spatial maps of each component to investigate regional specificity of between-group differences and treatment effects on within-network connectivity (for details, see Methods in Supplement 1).

Finally, Pearson correlation analyses were performed between modafinil-induced changes in Stroop task performance and within-network and between-network connectivity changes. The significance level was set to $p < .05$.

Results

Demographics and Clinical Assessments

Demographic and substance use characteristics are presented in Table 1. In the 6 months before the study, subjects in the AD group were drinking 11 units alcohol per day and had a mean AUDIT score of almost 29. The AD group did not differ from the HC group with regard to age or IQ. Alcohol dependence subjects smoked significantly more cigarettes than HC subjects. However, we did not include smoking as a covariate in subsequent analyses, because smoking behavior was related to alcohol consumption during the past months ($r = .56$, $p = .001$) and AUDIT scores ($r = .56$, $p = .001$). Therefore, including smoking as a covariate could remove variance explained by problematic drinking (overcorrection).

Stroop Color-Word Task Performance

A significant main effect of treatment ($F_{1,27} = 6.59$, $p = .02$) on Stroop interference scores was found (in AD decreasing from mean = 141.4 msec, SEM = 13.9 msec to mean = 118.9 msec, SEM = 16.1 msec; in HC decreasing from mean = 174.4 msec, SEM = 21.8 msec to mean = 112.3 msec, SEM = 15.8 msec; Figure 1), indicating beneficial effects of modafinil on cognitive control regardless of group membership. There was no main

Table 1. Demographic, Clinical, and Substance Use Characteristics

	Mean (SEM)			
	AD Group ($n = 15$)	HC Group ($n = 16$)	*t* (*df*)	*p* Value
Age	43.0 (2.4)	41.1 (1.8)	.6 (29)	.54
Education[a] (Number Within Category 2/3/4/5)	3/4/5/3	0/2/6/8	$\chi^2 = 6.0$ (4)	.20
IQ[b]	100.3 (3.4)	99.6 (3.1)	.2 (29)	.88
Total Alcohol in Last 6 Months (in Standard Units/Day)	11.4 (1.7)	.9 (.3)	6.3 (29)	<.001
AUDIT	28.7 (1.4)	5.8 (.8)	14.4 (29)	<.001
Cigarettes per Day	15.1 (3.5)	3.7 (1.6)	3.0 (29)	.01
Abstinence Duration (in Days)	36.5 (8.8)	NA	NA	NA

AD, alcohol dependence; AUDIT, Alcohol Use Disorder Identification Test; HC, healthy control; NA, not applicable.

[a]Measured using the International Standard Classification of Educational Degrees categories: 2 = lower secondary education, 3 = higher secondary education, 4 = postsecondary nontertiary education, 5 = first stage of tertiary education.

[b]Measured using the National Adult Reading Test.

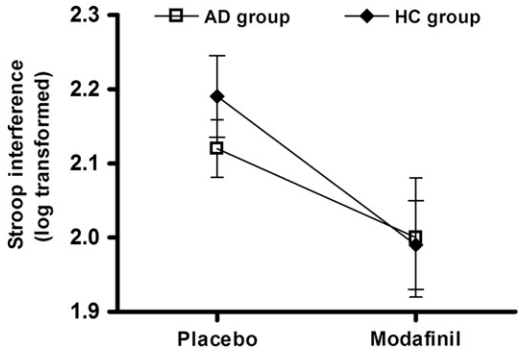

Figure 1. Stroop task interference scores in alcohol dependence (AD) and healthy control (HC), separate for placebo and modafinil. Stroop interference scores (log transformed: mean, SD) were plotted for AD and HC, separate for the placebo and modafinil condition. There was a significant main effect of treatment ($F_{1,27} = 6.56$, $p = .02$) on Stroop interference scores, indicating beneficial effects of modafinil on Stroop task performance regardless of group.

effect of group ($F_{1,27} = .27$, $p = .61$) or treatment by group interaction effect ($F_{1,27} = .80$, $p = .38$). With regard to number of errors made on the Stroop task, no main effect of treatment ($F_{1,27} = .45$, $p = .51$), main effect of group ($F_{1,27} = .44$, $p = .51$), or treatment by group interaction effect ($F_{1,27} = .02$, $p = .88$) was found.

Resting-State Functional Connectivity

Component Selection and Visualization. Within the independent resting-state networks identified by Group ICA, the DMN, the SN, and the CEN (separated into a left and right hemispheric component) were visually identified and selected for subsequent analyses in line with our hypotheses. A detailed overview of the regions within each functional network is provided in Figure 2 and Table S1 in Supplement 1.

Within-Network Functional Connectivity. No main effects of treatment, group, or treatment by group interaction effects were found with regard to the global within-network connectivity indices of any of the resting-state functional networks of interest (DMN, SN, CEN_left, and CEN_right). In addition, no effects of treatment, group, or interaction effects were found in the voxel-wise analysis on spatial maps for each network (see Results in Supplement 1).

Between-Network Functional Connectivity. We found a significant group by treatment interaction effect in the functional coupling between the DMN and SN ($F_{1,27} = 6.13$, $p = .02$), between the DMN and CEN_left ($F_{1,27} = 6.65$, $p = .02$), and between the DMN and CEN_right ($F_{1,27} = 6.23$, $p = .02$). Post hoc tests indicated that these interaction effects were all driven by a significant change in network coupling in AD subjects (DMN-SN: $F_{1,13} = 6.54$, $p = .02$; DMN-CEN_left: $F_{1,13} = 11.23$, $p < .01$; DMN-CEN_right: $F_{1,13} = 5.67$, $p = .03$), whereas no modafinil-induced changes in HC subjects were observed. Figure 3 shows that the correlation between DMN and SN and between DMN and CEN_left became more negative under modafinil in AD. The coupling between DMN and CEN_right was initially positive but was abolished after modafinil administration (Figure 3). In addition, post hoc tests indicated that none of the between-network connectivity measures were significantly different between AD and HC in the placebo condition. In the modafinil condition, however, the DMN and the SN ($F_{1,28} = 6.99$, $p = .01$) and the DMN and the CEN_right ($F_{1,28} = 5.21$, $p = .03$) were significantly more negatively coupled in AD compared with HC.

Brain-Behavior Associations. Correlation analyses revealed that modafinil-induced decreases in Stroop interference scores were significantly associated with increased negative coupling between DMN and SN in AD ($r = -.67$, $p < .01$; Figure 4A). Also, a trend toward a significant correlation between decreased DMN-CEN_right coupling and improvement in Stroop task performance was found in AD ($r = -.52$, $p = .06$; Figure 4B). No association between changes in DMN-CEN_left coupling and changes in interference scores was found in AD ($r = -.38$, $p = .18$). In HC, a trend toward a significant correlation between improvement in Stroop task interference scores and increased negative DMN-SN coupling was observed ($r = -.51$, $p = .06$).

Discussion

The current study aimed to investigate the effects of modafinil on interacting intrinsic large-scale brain networks and to relate this to changes in behavioral cognitive control. Overall, modafinil improved cognitive control reflected by decreased Stroop interference scores, regardless of having a diagnosis of alcohol dependence. However, modafinil-induced changes in between-network functional connectivity were only found in the AD group. Specifically, modafinil increased the anticorrelation between the DMN and the task-positive networks (SN, CEN). Moreover, strengthening of the negative functional coupling

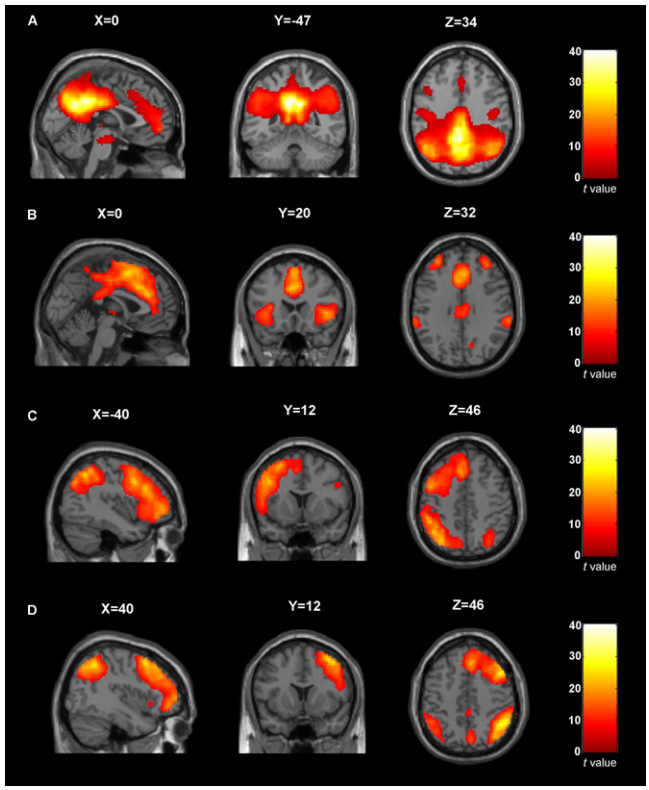

Figure 2. Resting-state networks of interest. Spatial characteristics of the resting-state networks of interest: **(A)** default mode network, **(B)** salience network, **(C)** left central executive network, and **(D)** right central executive network. Color bars represent voxel-wise *t* statistics thresholded for positive values. Statistical maps were thresholded $p < .05$ whole-brain family-wise error corrected.

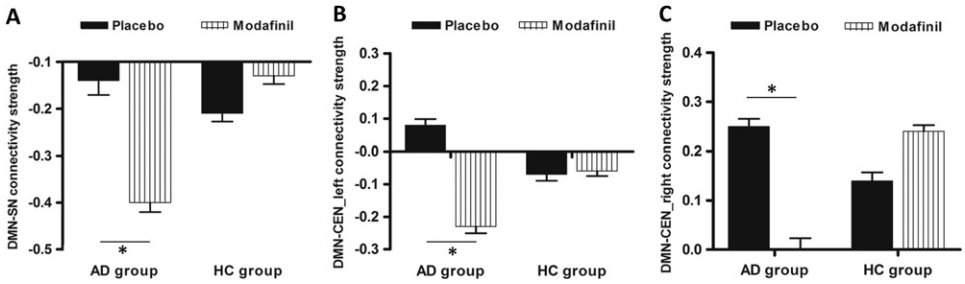

Figure 3. Modafinil-induced changes in between-network functional connectivity. **(A)** Modafinil administration significantly increased the negative coupling between the default mode network (DMN) and salience network (SN) ($F_{1,27} = 6.13$, $p = .02$), and **(B)** between the DMN and left central executive network (CEN_left) ($F_{1,27} = 6.65$, $p = .02$), and **(C)** significantly decreased coupling between the DMN and right central executive network (CEN_right) ($F_{1,27} = 6.23$, $p = .02$) in alcohol dependent (AD) patients only. No effects on between-network functional connectivity were found in the healthy control (HC) group*.

between the DMN and SN was associated with modafinil-induced improvements in cognitive control in alcohol-dependent patients. These results indicate that modafinil modulates the functional organization and communication of the brain, which translates into enhanced cognitive performance in AD.

The default mode network is involved in internally oriented cognition such as autobiographical memory retrieval, envisioning the future, or other self-referential mental representations (16). Brain regions involved in the DMN, such as the ventromedial PFC, PCC, amygdala, and hippocampus, play an important role in conditioning and reward-related processes implicated in substance dependence (38), including the processing of drug-related cues (39–41). Moreover, a recent study by Schulte *et al.* (42) demonstrated a reduced deactivation of the PCC during Stroop task performance in alcohol-dependent patients. In addition, regions implicated in the SN and the CEN are recruited by cognitive demanding tasks, including the Stroop task (43,44). Diminished functioning of regions involved in these networks, such as the dACC, DLPFC, and parietal cortex, has also been observed in alcohol-dependent patients in relationship to impaired cognitive control (45,46). Therefore, the currently observed modafinil effects on the competitive interaction between the DMN and task-positive networks could be of major importance in the context of alcohol dependence, because there is a strong need for executive brain networks to overrule activation of memory traces and processes of self-referencing when confronted with alcohol-related cues to resist the immediate rewarding properties of drinking alcohol.

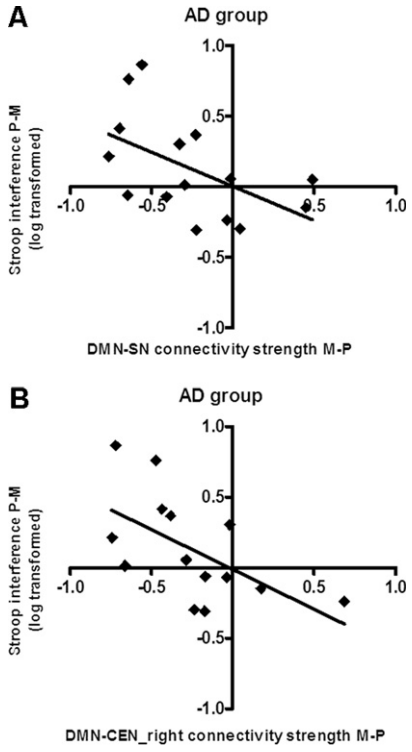

Figure 4. Brain-behavior relationship. **(A)** The modafinil-induced changes in default mode network (DMN)-salience network (SN) coupling were significantly correlated with changes in Stroop interference scores in alcohol dependent (AD) patients ($r = -.67$, $p < .01$); i.e., a stronger negative coupling between DMN and SN was associated with increased cognitive control after modafinil administration. **(B)** Also, a trend ($r = -.52$, $p = .06$) toward a significant relationship between decreases in DMN-right central executive network (CEN_right) coupling and decreases in Stroop interference scores was also observed in the AD group. M, modafinil; P, placebo.

Although previous fMRI studies have shown that modafinil administration results in a more efficient recruitment of the DLPFC, anterior insula, and dACC and enhances deactivation of the DMN during the performance of cognitive control tasks (23,24,26), the current study is the first to demonstrate specific effects of modafinil on the interaction between intrinsic large-scale functional networks. The currently observed modafinil-induced increases in the anticorrelation between the DMN and task-positive networks could indicate changes in the functional organization of the brain that can subsequently lead to a more efficient competitive relationship between networks involved in externally directed attention and internally focused thought processes when a demanding task is performed. Indeed, the increased negative coupling between the DMN and SN was associated with improvement in cognitive control in AD. This is in line with findings of a study by Kelly *et al.* (17) showing that the strength of the negative correlation between the DMN and task-positive resting-state networks is predictive of individual differences in the performance of a cognitive interference task. These previous observations, in addition to the current findings, stress the importance of communication between different large-scale networks in the brain underlying normal cognitive control function. The current data also emphasize that modafinil does not merely target some specific brain regions but that it has a much more general effect by affecting intrinsic functional relationships between large-scale brain systems. These widespread effects of modafinil seem to match the effects of modafinil on a broad range of neurotransmitters, including dopamine, noradrenaline, glutamate, serotonin, and gamma-aminobutyric

acid (47). It has been suggested that modafinil primarily exerts its effects on catecholamine transmission through inhibiting noradrenaline and dopamine transporters. Interestingly, a recent study by Dang *et al.* (48) showed that dopamine synthesis capacity is associated with the correlation between resting-state activity in the DMN and activity in a task-positive network (CEN), indicating that dopamine strengthens the functional interaction between these networks. These observations, together with the current findings, suggest that modafinil may modulate cognitive control by targeting dopaminergic influence on the properties of large-scale networks.

It should be noted here that, although we hypothesized that AD patients would show initial impaired cognitive control functions and altered within-network and between-network coupling relative to HC, at baseline, no significant differences in Stroop task performance and within-network and between-network coupling were found between the groups. However, modafinil-induced changes in coupling of the DMN with cognitive networks and correlation between these between-network connectivity changes and Stroop task performance were only found in the AD group. The initial (placebo) anticorrelation between the DMN and all three task-positive networks were nominally reduced in AD compared with HC, but these differences were nonsignificant, which may be explained by sample size limitations. Although the AD group showed no initial impairments in Stroop task performance, the modafinil-induced increases in anticorrelation between these networks in AD did result in improved cognitive control. The modafinil-induced improvement in Stroop task performance in HC could have emerged from modulation of other neural substrates or functional networks by modafinil that were beyond the scope of the present study, since no changes in within-network or between-network functional connectivity were observed in HC. Clearly, future research is needed examining other neural substrates or functional networks to further elucidate the neurobiological effects by which modafinil enhances cognitive functioning in AD and healthy volunteers.

The results of the current study should be viewed in light of some limitations. First, the groups were not well matched on smoking behavior. However, we decided not to include smoking behavior as a covariate because of its high association with alcohol-related problems and the risk of overcorrection resulting in a serious reduction of the variance in problematic drinking. Moreover, we showed that behavioral performance was not associated with smoking behavior. Second, three AD subjects tested positive for cannabis or benzodiazepines. Although most of these substances are detectable for up to 4 weeks in urine samples and self-reported use of these substances was in accordance with the requirement of being free of alcohol and drugs for at least 2 weeks, we cannot rule out the possibility that recent cannabis or benzodiazepine use confounded the results. However, post hoc analyses excluding these subjects revealed very similar results with regard to behavioral and imaging findings: all reported findings remained significant with the exception that modafinil-induced changes in DMN-CEN_right coupling in AD became a trend toward significance ($p = .07$ instead of $p = .02$) probably due to diminished power. In addition, the subjects were instructed to keep their eyes closed and to stay awake during the resting-state scan. An eyes-closed condition has previously been associated with a much stronger effect of another wakefulness-promoting substance (caffeine) on resting-state between-network connectivity of the DMN and a task-positive network compared with an eyes-open condition (49). Nonetheless, although all subjects included in the analyses reported that they remained awake during the resting-state scan, we could not objectively measure whether this was actually the case. We were not able to monitor sleeping during the experiment using a camera because of the eyes-closed condition. Future studies investigating modafinil effects on within-network and between-network resting-state connectivity could benefit by including a combination of an eyes-open and an eyes-closed resting-state condition. Finally, although modafinil significantly decreased the correlation between DMN and right CEN in alcohol-dependent patients, the initial (placebo) positive correlation between these networks seems counterintuitive. The lack of this initial anticorrelation may be explained by the fact that there are likely to be certain brain states in which network anticorrelations are more or less visible. For example, during performance of a cognitively demanding task, compared with a rest condition, this anticorrelation might be more visible due to the increased demand on task-positive networks and the need for deactivation of brain regions associated with mind wandering (DMN). Another brain state in which anticorrelations are more visible is a resting-state condition while under influence of substances (e.g., caffeine [49]) known to enhance wakefulness and attention, functions that rely on activation in task-positive networks. Given the competitive relationship between the DMN and task-positive networks, increased drug-induced recruitment of task-positive activation would be expected to be accompanied by a reduction in DMN activation. Therefore, the negative association between the DMN and task-positive networks might initially have been less pronounced in our study (reflected by a positive correlation or a smaller negative correlation), whereas administration of the wakefulness-promoting and cognitive-enhancing compound modafinil resulted in an enhanced intrinsic competitive relationship (correlation coefficients become more negative) in AD subjects, which was, in turn, predictive of improvement in performance when cognitive demand was imposed on the subjects during the Stroop task.

Taken together, our findings show that modafinil exerts its effects not by merely enhancing activation of individual brain regions, but by targeting important intrinsic large-scale functional networks of the brain. Moreover, these changes in between-network functional connectivity were associated with a modafinil-induced improvement in cognitive control, which is one of the core functions known to be impaired in alcohol dependence. Therefore, the current study provides a neurobiological rationale for implementing modafinil as an adjunct in the treatment of alcohol dependence. Clinical studies are needed to substantiate this promise.

We thank the Netherlands Organization for Scientific Research for their financial support (ZonMW Grant 31160003).

The authors report no biomedical financial interests or potential conflicts of interest.

Netherlands Trial Register: Impulsivity, a Risk Factor in Relapse to Substance Use Disorder: Investigating Neural Substrates Before and After Pharmacological Challenges. http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=2122; NTR2122.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2012.12.025.

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