ARCHIVAL REPORT

Effects of Modafinil on Neural Correlates of Response Inhibition in Alcohol-Dependent Patients

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Background: Impaired response inhibition is a key feature of patients with alcohol dependence. Improving impulse control is a promising target for the treatment of alcohol dependence. The pharmacologic agent modafinil enhances cognitive control functions in both healthy subjects and in patients with various psychiatric disorders. However, very little is known about the underlying neural correlates of improvements in response inhibition following modafinil.

Methods: We conducted a randomized, double-blind, placebo-controlled, crossover study using functional magnetic resonance imaging with a stop signal task to examine effects of a single dose of modafinil (200 mg) on response inhibition and underlying neural correlates in abstinent alcohol-dependent patients (AD) ($n = 16$) and healthy control subjects ($n = 16$).

Results: Within the AD group modafinil administration improved response inhibition (reflected by the stop signal reaction time [SSRT]) in subjects with initial poor response inhibition, whereas response inhibition was diminished in better performing subjects. In AD patients with initial poor response inhibition, modafinil-induced SSRT improvement was accompanied by greater activation in the thalamus and supplementary motor area (SMA) and reduced connectivity between the thalamus and the primary motor cortex. In addition, the relationship between baseline response inhibition and modafinil-induced SSRT improvement was mediated by these changes in thalamus and SMA activation.

Conclusions: These findings indicate that modafinil can improve response inhibition in alcohol-dependent patients through its effect on thalamus and SMA function but only in subjects with poor baseline response inhibition. Therefore, baseline levels of response inhibition should be taken into account when considering treatment with modafinil in AD.

Key Words: Alcohol dependence, functional MRI, impulsivity, modafinil, response inhibition, thalamus

Relapse is the rule rather than the exception in alcohol-dependent patients seeking treatment. Psychosocial treatments are only moderately successful, because many patients fail to respond to the interventions and only a minority of those that do respond succeed in maintaining prolonged abstinence (1). Treatment success may be hampered by cognitive impairments associated with chronic alcohol abuse (2), as diminished impulse control predicts treatment outcome and relapse into alcohol abuse (3–7). Therefore, pharmacologic improvement of impulse control using a cognitive enhancer may constitute an important treatment option in alcohol dependence.

A promising cognitive enhancer is modafinil, a wakefulness-promoting drug approved for treatment of narcolepsy. In addition, modafinil is widely used to enhance cognition (8–10). Modafinil shows beneficial effects on cognitive functions in healthy individuals (11) and in patients with schizophrenia (12–15) and attention-deficit/hyperactivity disorder (16). With regard to addictive behaviors, modafinil reduces impulsivity in patients with methamphetamine dependence (17) and pathological gambling (18), especially on measures of response inhibition. Response inhibition is broadly defined as the ability to inhibit a prepotent response (19) and can be assessed using neurocognitive tasks such as the stop signal task and the go/no-go task (20). However, previous work suggests that modafinil does not improve response inhibition in all individuals but is only effective in humans and rodents with poor response inhibition at baseline (18,21), suggesting that baseline response inhibition mediates the effect of modafinil on response inhibition.

Enhanced response inhibition may, in part, explain the beneficial effects of modafinil in the treatment of cocaine dependence (22,23) and methamphetamine dependence (24). Whether modafinil also improves response inhibition in nonstimulant addictions like alcohol dependence has not yet been investigated. Moreover, only one study has yet been published investigating the neural mechanisms underlying enhanced cognitive functioning in substance-dependent individuals. Ghahremani *et al.* (25) showed that a single dose of modafinil improves learning by stimulating prefrontal activity in methamphetamine-dependent patients. However, the neural correlates of modafinil-mediated improvement in response inhibition remain to be elucidated, which would increase not only our insight of neurobiological mechanisms of distorted impulse control but also our understanding of the treatment of psychiatric conditions such as alcohol dependence.

Therefore, the current study aimed to investigate the effects of a single dose of modafinil (200 mg) on response inhibition and its neural correlates in alcohol-dependent patients compared with healthy volunteers using functional magnetic resonance imaging (fMRI). A single dose was chosen based on prior studies showing significant effects of a single dose of this magnitude on cognition and related brain activation as measured with fMRI (12,14–16,25). To assess response inhibition, the stop signal task was applied, which measures the ability to stop an already initiated response (26). Key brain regions involved in response inhibition during a stop signal task are the inferior frontal gyrus (IFG), the presupplementary

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motor cortex (SMA), thalamic regions including the thalamus and the subthalamic nucleus (STN), and the striatum. A so-called hyperdirect-indirect model (27) related to the stop signal paradigm has been proposed in which projections from the IFG or pre-SMA to the globus pallidus, via the striatum or the STN, and then back to the cortex (primary motor cortex [M1]) via the thalamus are thought to be crucial for response inhibition (28,29). Therefore, the effects of modafinil on activation of and connectivity between these specific brain regions were examined in the current study. Given earlier findings that modafinil is especially effective in individuals with poor response inhibition, our second aim was to examine whether beneficial effects of modafinil are indeed most pronounced in poorly performing alcohol-dependent patients.

Methods and Materials

Subjects

Twenty male subjects meeting DSM-IV (30) 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 Supplemental Methods in Supplement 1. Four AD and two HC subjects were excluded from analyses due to either too many omission errors on go trials or excessive head motion during scanning. The remaining data from 32 participants (16 AD, 16 HC) were used in statistical analyses. To avoid confounding due to nicotine withdrawal (31), smokers were allowed to smoke freely before the experiment (satiation during fMRI).

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 has 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 (200 mg) or placebo tablets. In the second session, subjects were crossed over to receive the opposite medication. Eight AD subjects and eight HC subjects received modafinil in the first session and placebo in the second session. Medication was administered 2 hours before fMRI, because peak plasma levels occur at 2 to 4 hours after a single dose (32).

Clinical Assessments

All subjects were screened for the presence of Axis I psychiatric disorders using the Mini International Neuropsychiatric Interview-Plus (33). Education level was classified according to the International Standard Classification of Educational Degrees (34). General intelligence (IQ) was assessed using the National Adult Reading Test (35). Alcohol and drug consumption during the preceding 6 months was quantified using the Time Line Follow Back method (36). In addition, the Alcohol Use Disorder Identification Test (AUDIT) was used to identify harmful patterns of alcohol consumption (37). The Short Alcohol Withdrawal Scale, a 10-item self-report questionnaire to measure alcohol withdrawal symptoms (with a total score ranging from 0 to 30), was administered in both sessions (38). To investigate modafinil-induced neurophysiologic side effects and craving, self-report questionnaires were administered in both sessions. A checklist was used assessing 15 possible side effects and potential stimulant effects of modafinil including symptoms like headache, palpitations, nervousness, nausea, sweating, and a dry mouth. Subjects were asked to rate side effects on a scale from 0 (not at all) to 4 (severely). Craving was assessed using the Alcohol Urge Questionnaire (39).

Stop Signal Task

Subjects performed a stop signal task including go and stop trials while fMRI images were obtained (40). For a detailed description of the task, see Supplement 1. Briefly, during the go trials, the subjects had to respond as fast and accurately as possible by pressing a button with their left or right index fingers in response to an airplane facing either to the left or right. Occasionally, a stop stimulus was presented and the subjects were instructed to try to inhibit the go response. By adjusting the interval between the go and stop stimulus, the stop signal delay (SSD), the difficulty of stopping was varied using a staircase procedure (41), which converged upon a critical SSD representing the time delay required for the subjects to successfully stop their response on approximately 50% of the stop trials. The time required for the stop signal to be successfully processed, the stop signal reaction time (SSRT), was computed by subtracting the critical SSD from the mean go reaction time. A longer SSRT indicates poorer response inhibition.

Imaging Protocol

Magnetic resonance imaging (MRI) data were obtained using a 3.0 T Intera MRI scanner (Philips Healthcare, Best, The Netherlands) equipped with a SENSE eight-channel receiver head coil. A gradient-echo echo planar image 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 approximately 365 images. 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 image data.

Data Analysis

Behavioral Data. Demographic, self-report, and stop signal task performance data were analyzed using the Statistical Package for the Social Sciences (SPSS 16; Chicago, Illinois). Differences in baseline characteristics between groups were analyzed using independent *t* tests. A repeated measures analysis of variance was conducted to assess self-reported effects of modafinil and stop signal task performance with treatment (modafinil vs. placebo) modeled as a within-subject factor and group (AD vs. HC) and session order as between-subjects factors. Modafinil-induced improvement in SSRT was defined as SSRT placebo minus SSRT modafinil ($SSRT_p - SSRT_m$) with positive values indicating improvement. The relation between modafinil-induced improvement with self-report data and placebo SSRT was investigated for both groups (AD and HC) using a Pearson correlation including session order as a covariate. The significance level was set to $p < .05$.

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

Four main types of trial outcome were distinguished: go success, omission, stop success (SS), and stop error (SE) for each session. In a first-level, single-subject, fixed-effects analysis, regressors were constructed by convolving the onsets of the go stimulus with a canonical hemodynamic response function to model each outcome type. To account for low-frequency signal drift, a high-pass filter (1/128 Hz) was applied. Next, contrasts SS > SE were computed for each session to examine regional brain activation related to successful versus unsuccessful response inhibition. These con-

trast images were then entered into a second-level, random-effects analysis using a flexible factorial design to investigate within-group effects of medication and group by medication interaction effects. Independent *t* tests were used to compare between-group effects on placebo and modafinil, including session order as a covariate. A whole-brain linear regression was used to explore regions showing modafinil-induced changes in activation (SS > SE, modafinil > placebo) that varied linearly with improvement in SSRT, including session order as a covariate. To assess connectivity between brain regions for SS > SE that interacted with modafinil administration, we used a generalized form of psychophysiological interaction analyses (see Supplement 1 for details on this method).

We focused our imaging analyses on regions of interest (ROIs) that have been implicated in the hyperdirect-indirect model of response inhibition including the IFG, a motor region including M1 and (pre-)SMA; a striatal region including caudate, putamen, and globus pallidus; and a thalamic region including the thalamus and STN (27–29,42). The WFU PickAtlas Tool v2.4 (43) was used to create four separate masks containing these bilateral ROIs. Only significant brain activations that survived family-wise error correction for multiple comparisons on the voxel level within the ROIs using a small volume correction (44), or across the entire brain for regions not a priori of interest, are reported in the Results section. For exploratory purposes, results significant at a more liberal (uncorrected) threshold are reported in the Supplemental Results in Supplement 1.

Results

Demographics and Clinical Assessments

Demographic, self-report, and substance use characteristics are presented in Table 1. The AD group did not differ from the HC group with regard to age, educational level, or IQ. Alcohol dependence subjects smoked significantly more cigarettes than HC subjects. We did not include smoking as a covariate in subsequent analyses, because smoking behavior was related to alcohol consumption during the past 6 months ($r = .47, p = .01$) and AUDIT scores ($r = .54$, $p = .001$). Therefore, including smoking as a covariate could also remove variance explained by problematic drinking.

No adverse events were reported and self-reported withdrawal symptoms were low (Table 2). Modafinil did not induce side effects and had no effect on self-reported craving (Table 2).

Stop Signal Task Performance

There was no significant group, treatment, or treatment by group interaction effect on any of the performance measures (Table 2). Within the AD group, modafinil (compared with placebo) did not affect SSRT or other performance measures. However, in the HC group, modafinil significantly decreased mean reaction time on go trials [$t(15) = 2.16, p = .05$] but had no effect on other performance measures.

A correlation analysis revealed that modafinil-induced improvement in SSRT was significantly correlated with baseline SSRT ($SSRT_p$), within AD subjects ($r = .56, p = .03$) and within HC subjects ($r = .63$, $p = .01$). Subjects with poor baseline response inhibition benefited from modafinil in terms of SSRT improvement and thus became less impulsive, whereas better performing subjects on baseline became more impulsive under modafinil compared with placebo. A median split based on $SSRT_p$ revealed that within the AD group, response inhibition improved significantly more by modafinil administration in subjects with poor initial SSRT performance compared with subjects with better initial $SSRT_p$ performance [$F(1,12) = 6.74$, $p = .02$] (Figure 1). In contrast, in HC, no differences in modafinil-induced changes in response inhibition were found between subjects with low and high $SSRT_p$ [$F(1,12) = .47$, $p = .51$].

Neither $SSRT_p$ nor SSRT improvement were associated with severity of alcohol-related problems (AUDIT), number of cigarettes smoked per day, amount of alcohol consumed in the past 6 months, abstinence period, craving (Alcohol Urge Questionnaire scores), and physical symptoms (side effects).

Regional Brain Activations

Main effects (across sessions and across groups) of SS and SE trials are reported in the Supplemental Results in Supplement 1 (Figure S1 in Supplement 1). In addition, results of one-sample *t* tests for placebo and modafinil, separately for AD and HC, can be found in the Supplemental Results in Supplement 1 (Table S1 in Supplement 1).

Task-Related Brain Activation Within and Between Groups. For the SS > SE contrast, a cluster in the left putamen showed a significant group by treatment interaction effect. Post hoc tests revealed that this effect was driven by a significant increase in activation of the left putamen in AD after modafinil administration compared with the placebo condition (Figure S2 in Supplement 1), whereas modafinil had no effect on brain activation in HC. In addition, no differences in regional brain activation between the groups were found within the placebo and modafinil condition.

Regression Analysis. A regression analysis of differences in brain activation (SS > SE, modafinil > placebo) against the improvement in SSRT ($SSRT_p - SSRT_m$) revealed a positive correlation in the left SMA and the right ventrolateral thalamus within the AD group. Inspection of the scatterplot (Figure 2) indicates that subjects with improved performance showed an

Table 1. Demographics, Clinical, and Substance Use Characteristics

	Mean (SD)			
	AD Group ($n = 16$)	HC Group ($n = 16$)	*t* (*df*)	*p* Value
Age	42.9 (9.4)	41.7 (8.2)	.4 (30)	.69
Education[a]	3.3 (1.3)	4.1 (1.1)	−1.7 (30)	.09
IQ[b]	99.6 (12.0)	100.5 (11.3)	−.2 (30)	.83
Alcohol in Last 6 Months (in Standard Units/Day)	11.9 (8.1)	1.0 (1.1)	5.4 (30)	<.001
AUDIT	28.4 (5.5)	6.3 (3.3)	13.8 (30)	<.001
Cigarettes per Day	15.0 (12.9)	4.6 (7.5)	2.8 (30)	.01
Total Cannabis Use in Last 6 Months (in Grams)	11.7 (18.8)	NA	NA	NA

AD, alcohol dependence; AUDIT, Alcohol Use Disorder Identification Test; HC, healthy control subjects; IQ, intelligence quotient; NA, not applicable; SD, standard deviation.

[a]Measured using the International Standard Classification of Educational Degrees.

[b]Measured using the National Adult Reading Test.

Table 2. Clinical Characteristics and Stop Signal Task Performance in the Modafinil and the Placebo Condition

		Mean (SD)			
	Session	AD Group ($n = 16$)	HC Group ($n = 16$)	F (df)[a]	p Value
Self-Report Measures					
Withdrawal symptoms[b]	Placebo	4.7 (4.3)	1.6 (2.3)	.90 (1,28)	.35
	Modafinil	4.1 (3.9)	1.7 (2.5)		
Side effects[c]	Placebo	2.5 (2.0)	2.6 (3.0)	.00 (1,28)	.99
	Modafinil	2.6 (3.9)	2.6 (3.0)		
Craving for alcohol[d]	Placebo	9.9 (9.2)	6.3 (6.9)	1.97 (1,28)	.17
	Modafinil	8.1 (8.6)	5.9 (8.0)		
Stop Signal Task Performance					
SSRT, msec	Placebo	237.1 (34.5)	258.9 (37.7)	.46 (1,28)	.51
	Modafinil	240.2 (29.5)	254.1 (34.7)		
% Correct stop trials	Placebo	51.3 (3.0)	52.08 (2.0)	1.07 (1,28)	.31
	Modafinil	50.9 (2.8)	50.8 (2.1)		
% Correct go trials	Placebo	98.4 (1.4)	98.3 (1.3)	.05 (1,28)	.82
	Modafinil	98.9 (.9)	98.7 (1.5)		
Mean RT go, msec[e]	Placebo	537.6 (83.9)	565.2 (77.5)	2.25 (1,28)	.15
	Modafinil	538.8 (86.5)	532.9 (81.6)		

AD, alcohol dependence; HC, healthy control subjects; SSRT, stop signal reaction time; RT, reaction time.

[a]Results are presented for the treatment (placebo versus modafinil) × group (AD vs. HC) interaction effect. Within groups, there was only a significant effect of treatment on mean RT go trials in the HC group.

[b]Measured using the Short Alcohol Withdrawal Scale.

[c]Measured using a 15-item side effects checklist.

[d]Measured using the Alcohol Urge Questionnaire.

[e]Mean reaction time on go trials.

increase in activation of these brain areas, whereas subjects with worsened performance showed a decrease. Post hoc correlations of SSRT improvement with changes in brain activation separately for SS and SE trials indicated that SSRT improvement was associated with a modafinil-induced decrease in SMA activation during SE trials but not with an increase in activation during SS trials. With regard to the thalamus, a combination of increased activation during SS trials and decreased activation during SE trials was associated with greater SSRT improvement. No negative correlations were found in AD. Within the HC group, regression analysis revealed no significant positive or negative correlations between improvement in SSRT and activity changes.

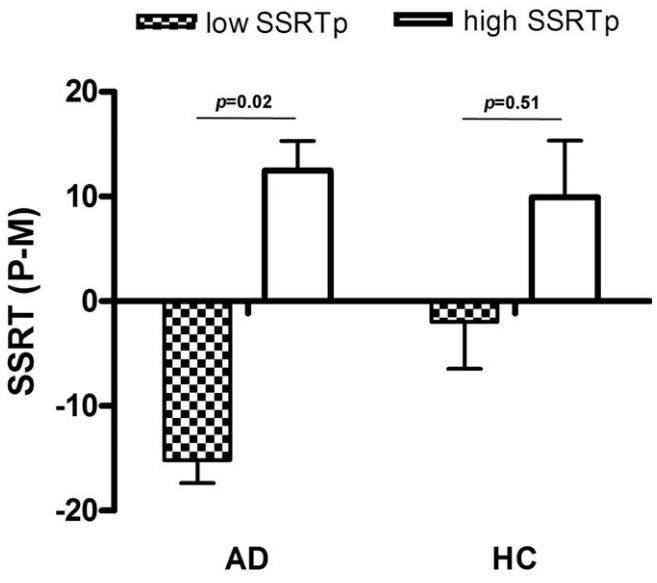

Figure 1. Stop signal reaction time (SSRT) improvement (SSRT placebo minus modafinil [P−M]) in alcohol dependent (AD) and healthy control subjects (HC) separately for subjects with poor baseline response inhibition (high SSRT placebo [SSRTp]) and subjects with good baseline response inhibition (low SSRTp). Significant differences were found in AD in which poor performing subjects improved their response inhibition after modafinil administration, whereas better performing subjects deteriorated after modafinil administration.

For the AD group, we extracted parameter estimates of activity change (SS > SE, modafinil > placebo) in the thalamus and SMA to further examine correlations with behavioral measures. Activity change in the SMA ($r = .72$, $p < .01$) and the thalamus ($r = .53$, $p = .04$) correlated significantly with baseline response inhibition ($SSRT_p$), indicating that AD subjects that initially performed worse showed greater modafinil-induced activity increase within these regions (Figure 2). No correlations between these activity changes and other stop signal task performance measures were found.

Effective Connectivity. For functional connectivity analysis, the left SMA (peak MNI coordinates: −6, −13, 58) and right thalamus (peak MNI coordinates: 9, −10, 4) were defined as seed regions. To examine whether connectivity changes of these regions with other brain regions were also associated with SSRT improvement, we regressed the AD subjects' psychophysiological interaction contrast images against their SSRT improvement. For the SMA, we found no functional connectivity changes associated with SSRT improvement. For the thalamus, there was a negative correlation between connectivity changes of the thalamus with the left precentral gyrus (M1) and SSRT improvement (Figure S3 in Supplement 1) but only when correcting for multiple comparisons within masks containing unilateral regions of interest instead of bilaterally. This indicates that improvement in SSRT is accompanied by a decreased coupling of the right ventrolateral thalamus with the left M1. The parameter estimate of the connectivity change between the thalamus and M1 was not correlated with $SSRT_p$.

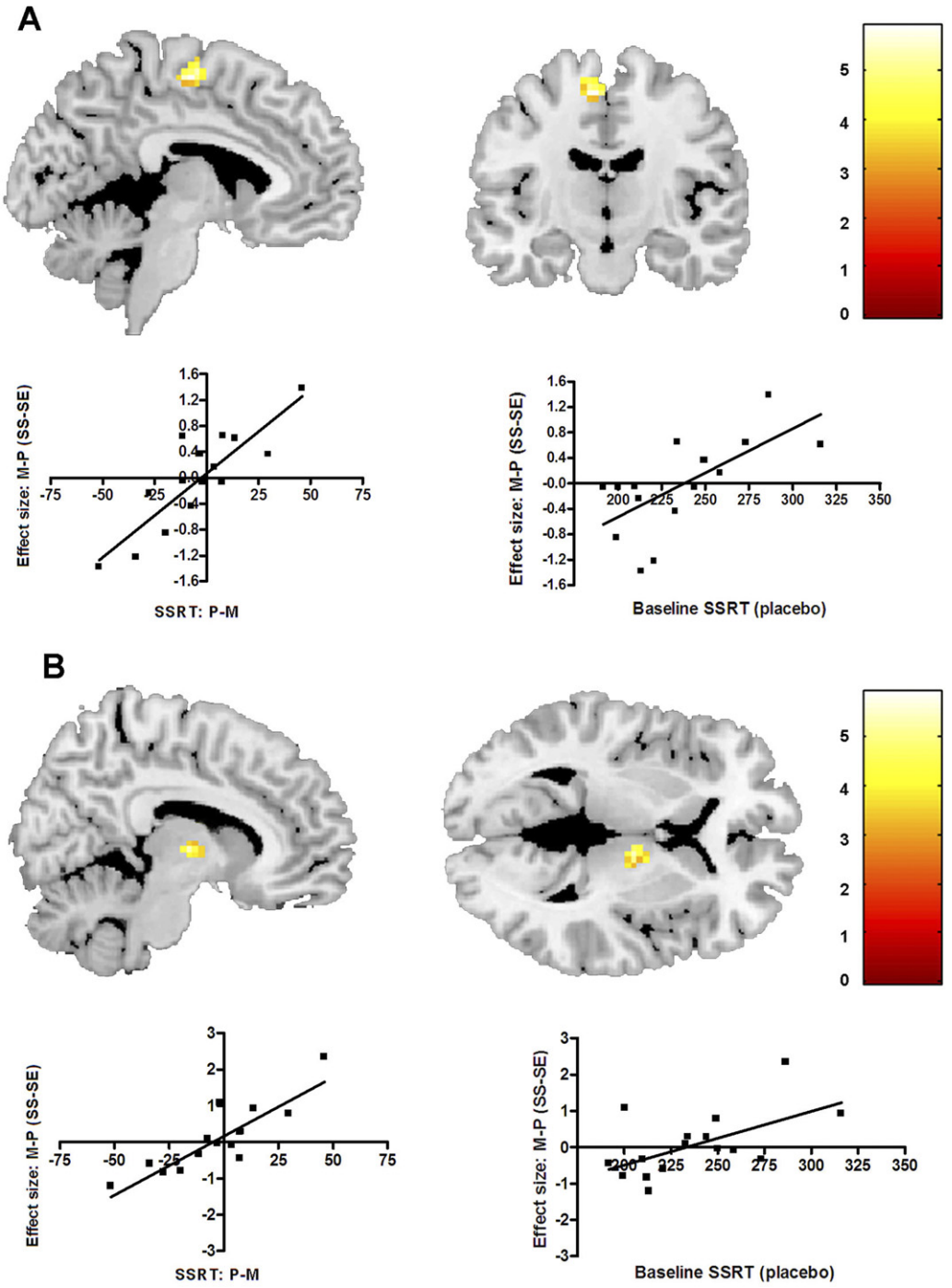

Figure 2. Modafinil-induced activity changes (parameter estimates for modafinil minus placebo (M−P), stop success [SS] − stop error [SE]) in alcohol dependent (AD) subjects associated with response inhibition in **(A)** the left supplementary motor cortex (SMA) and **(B)** the right ventrolateral thalamus. Activity increases both in the left SMA and right thalamus were significantly correlated with improvement in response inhibition (stop signal reaction time [SSRT]: placebo minus modafinil [P−M]) and baseline response inhibition (SSRT placebo). The color bar represents voxel T value.

Mediation Analysis. Because $SSRT_p$ correlated with SSRT improvement and both were associated with modafinil-induced increase in SMA and thalamus activation, we investigated whether the observed relationship between baseline response inhibition ($SSRT_p$) and modafinil-induced improvement in response inhibition ($SSRT_p > SSRT_m$) was actually caused by these modafinil-induced brain activity changes using post hoc mediation analyses (for details of the analyses, see Supplement 1). Mediation analyses showed that the relationship between $SSRT_p$ and SSRT improvement was almost completely mediated by increased activation of the SMA and thalamus after modafinil administration (Figure 3).

Discussion

This study demonstrates that modafinil can improve response inhibition by modulating activation in key regions involved in suc-

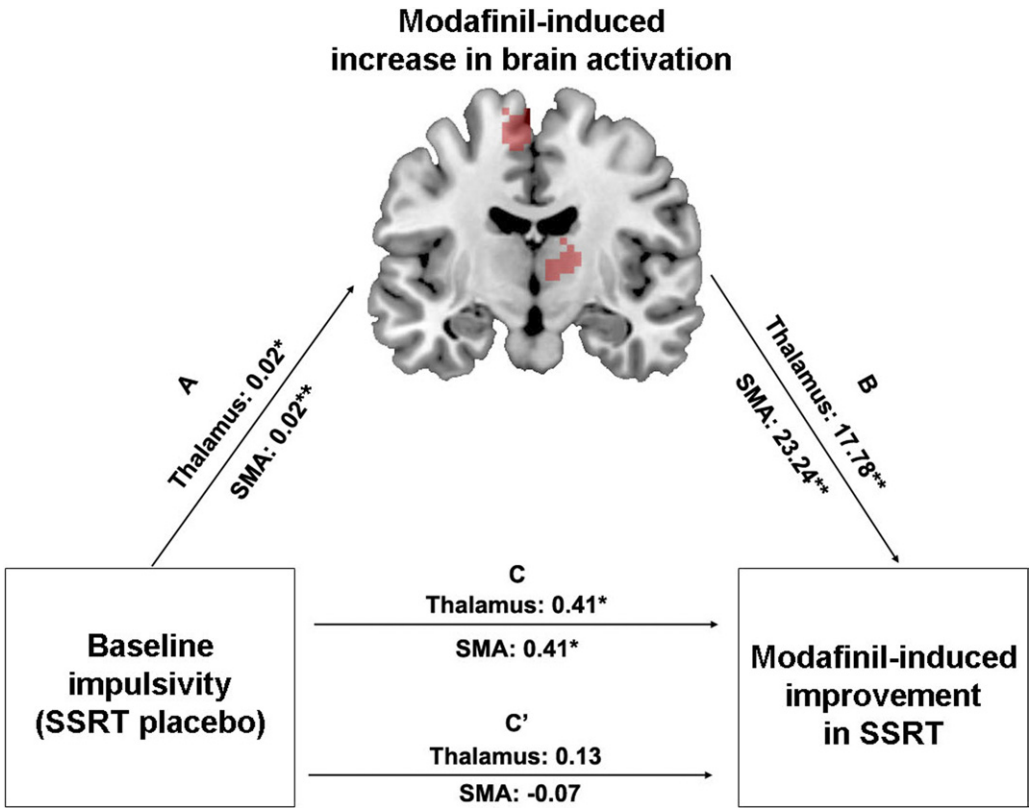

Figure 3. Path analysis showing that the relationship between baseline response inhibition (stop signal reaction time [SSRT] placebo) and modafinil-induced improvement in SSRT (path C) is almost completely mediated by modafinil-induced changes in right ventrolateral thalamus and left supplementary motor cortex (SMA) activation (path C′: direct relation between SSRT placebo and SSRT improvement when corrected for mediator). Bootstrap tests for mediation effects (path C minus path C′) were significant for both the thalamus and SMA. *$p < .05$ and **$p < .01$ for path coefficients.

cessful inhibition (SMA and thalamus) but only in alcohol-dependent patients that show poor initial response inhibition. In contrast, response inhibition in better performing subjects deteriorated after receiving modafinil. These observations are in line with findings of modafinil-induced improvements and deteriorations in response inhibition in subjects with low and high levels of response inhibition at baseline, respectively, in studies with pathological gamblers (18) and rodents (21). The observation that positive effects of modafinil are only found in subjects initially performing poorly is consistent with findings from a wider range of cognitive functioning. For example, modafinil was found to be effective only in healthy individuals and patients with schizophrenia and methamphetamine dependence who show poor baseline performance on working memory (14,45), cognitive control (12), and visual attention tasks (46).

Although the exact pharmacological mechanism of action of modafinil remains to be elucidated, it has been suggested that modafinil primarily exerts its effects on catecholamine (including dopamine and noradrenalin) transmission (47). The current findings of a modafinil-induced improvement in response inhibition in poorly performing AD subjects, together with a modafinil-induced deterioration in response inhibition in better performing subjects, are in line with an inverted U-shaped relationship between catecholamine neurotransmitter levels and cognitive performance (48). This inverted U-shaped curve implies that there is an optimum for catecholamine neurotransmitter levels to efficiently execute cognitive tasks. Future single-photon emission computed tomography or positron emission tomography using dopamine receptor ligands could clarify this proposed relationship between response inhibition and modafinil-induced changes in catecholamine neurotransmission.

Modafinil-induced improvement in response inhibition was accompanied by modulation of brain activation in the right ventrolateral thalamus and the left SMA in AD patients. Furthermore, modafinil-induced activity changes in these brain regions mediated the relationship between baseline SSRT and improvement in SSRT, indicating that activity changes within these brain regions were (largely) responsible for SSRT improvements observed in poorly performing AD patients. These findings are consistent with previous studies showing that both SMA and thalamus play an important role in the interruption of ongoing responses (e.g., [49]). The SMA is part of the motor cortex and is involved in planning and coordination of complex movements. Neuroimaging studies using the stop signal task have shown the pre-SMA to be critically involved in inhibiting a response (49,50), whereas the SMA seemed to be more active during failed inhibition (49–51). Indeed, when we examined the correlation between SSRT improvement and modafinil-induced increase in SMA activation during response inhibition (SS > SE) more closely, a decrease in SMA activation during SE trials, and not an increase during SS trials, was responsible for the observed correlation, indicating more efficient error processing during failed inhibitions. The ventrolateral nucleus of the thalamus (also termed the motor thalamus) has direct connections with the motor cortex. When a motor command is initiated, the thalamus is disinhibited, which increases thalamocortical output that activates the motor cortex. However, when a motor response needs to be inhibited, output from the thalamus to the motor cortex is sup-

pressed (27). Based on these observations, it is expected that modafinil-induced increased activation in the ventrolateral thalamus would be associated with a reduced capability to inhibit an ongoing response instead of the observed improvement of response inhibition. However, thalamus activation as identified using fMRI may represent either excitatory or inhibitory neural activity. Importantly, our connectivity analyses revealed that SSRT improvement was accompanied by a reduced functional coupling between thalamus and M1, consistent with the assumption that for successful inhibition, output from the thalamus to the motor cortex needs to be suppressed. These findings suggest that modafinil exerts its effect directly on the thalamus, resulting in subsequent changes in functional connections of the thalamus with other brain regions. Previous work has indeed indicated that modafinil elevates glutamate and noradrenalin levels in the thalamus in rodents (47) and increases cerebral blood flow in the thalamus in humans (52), supporting the hypothesis of the thalamus being a primary target for modafinil to exert its effects.

In the AD group, regardless of high versus low levels of response inhibition, modafinil was associated with increased activation in the left putamen, but this was not related to SSRT improvement. This may indicate a broader effect of modafinil on striatal activation in AD. Indeed, modafinil induces dopamine release in the striatum (53), which is suggestive for stimulant properties of modafinil. For that reason, we performed post hoc correlation analyses of modafinil-induced putamen activity with subjective reinforcing effects in AD. However, modafinil-induced increase in putamen activity was not associated with stimulant effects or craving.

Our results should be viewed in light of some limitations. First, four 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 in the stop signal task (see Supplemental Results in Supplement 1). A second limitation is that baseline response inhibition was defined by the SSRT in the placebo condition instead of a separate independent baseline SSRT measure and therefore the current behavioral findings could be biased by regression toward the mean. A major factor affecting the amount of regression toward the mean is the correlation between SSRT in the two sessions: the smaller the correlation, the greater the amount of regression toward the mean. Given the high correlation between $SSRT_p$ and $SSRT_m$ in AD ($r = .73$, $p = .001$) and the relatively low correlation between the $SSRT_p$ and $SSRT_m$ in HC ($r = .36$, $p = .17$) in the current study, in addition to findings of differential effects of modafinil in poor and better performing subjects in previous studies, we believe that our results reflect true differential of modafinil effects in AD. This was supported by the observed modafinil-induced brain activity changes in AD. Furthermore, if the observed differential effects were merely caused by a regression toward the mean, regression toward the mean would be expected regardless of session order allocation (placebo first or modafinil first), i.e., SSRT in the first session would be correlated with SSRT improvement regardless of receiving placebo or modafinil in the first session. Instead, $SSRT_m$ was not correlated with SSRT improvement (regardless of receiving modafinil in the first or second session): a low and nonsignificant correlation was observed in the AD group between $SSRT_m$ and the SSRT change score ($r = -.18$, $p = .52$). Nonetheless, future studies should include an independent baseline impulsivity measure to control for this potential confound. A final limitation is that no measures for other domains of impulsivity, such as impulsive decision making, were included, thereby limiting the generalizability of the current findings. Especially given the fact that there is minimal overlap in underlying cognitive and neural processes involved in these different aspects of impulsivity (19,54), modafinil effects on other domains of impulsivity remain to be elucidated.

Despite some limitations, the current study provides new insights in the neurobiological mechanisms responsible for the modulating effect of modafinil on impulsivity in alcohol-dependent patients: the effect of modafinil on inhibitory control is mediated by functional changes in brain regions specifically involved in motor response inhibition. In addition, the current observations demonstrate the importance of personalized medicine: the behavioral and neurophysiologic effects of modafinil in AD are dependent on baseline levels of response inhibition and therefore baseline cognitive performance should be taken into account to obtain an optimal effect, i.e., to have high success rates and to avoid iatrogenic deterioration.

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Nederlands 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.

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