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Assessment of brain activity during memory encoding in a narcolepsy patient on and off modafinil using normative fMRI data

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We present behavioral and functional magnetic resonance imaging (fMRI) findings of a 20-year-old female with narcolepsy who completed a standardized fMRI-adapted face memory task both 'off' and 'on' modafinil compared to a normative sample ($N = 38$). The patient showed poor recognition performance off modafinil ($z = -2.03$) but intact performance on modafinil ($z = 0.78$). fMRI results showed atypical activation during memory encoding off modafinil, with frontal lobe hypoactivity, but hippocampal hyperactivity, whereas all brain regions showed more normalized activation on modafinil. Results from this limited study suggest hippocampal and frontal alterations in individuals with narcolepsy. Further, the results suggest the hypothesis that modafinil may affect brain activation in some people with narcolepsy.

Keywords: Narcolepsy; Memory encoding; Modafinil; Normative data; fMRI; Hippocampus.

Occurring with a prevalence of one in 2000 according to population-based epidemiologic studies in North America and Europe (Mignot, 1998; Ohayon, Priest, Zulley, Smirne, & Paiva, 2002), narcolepsy is characterized by rapid eye movement (REM) sleep dysregulation, excessive daytime sleepiness, cataplexy, hypnagogic and hypnopompic hallucinations, sleep paralysis, and irresistible sudden-onset sleep episodes (Chakravorty & Rye, 2003; Mitler & Hayduk, 2002). A majority of narcolepsy cases have an onset between ages 15 and 35 years, and men and women are affected equally (Naumann & Daum, 2003).

Narcolepsy is associated with dysregulation in the production or function of hypocretin (also known as orexin) a hypothalamic peptide that aids in the regulation of the sleep–wake cycle, attention, and emotion (Kroeger & de Lecea, 2009). Hypocretin dysregulation is associated with decreased hypothalamic projection to several cortical regions (Overeem et al., 2001, 2003) and reduced gray matter volumes of the hypothalamus and inferior frontal and temporal lobes (Buskova, Vaneckova, Sonka, Seidl, & Nevsimalova, 2006; Kaufmann, Schuld, Pollmacher, & Auer, 2002) Decreased gray matter volume in narcolepsy may be associated with subsequent difficulties in arousal-related processes that mediate attentional functioning (Kaufmann et al., 2002).

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The treatment of narcolepsy includes sodium oxybate and modafinil. The mechanism of action of sodium oxybate is unclear, although it may be a gamma butyric acid receptor B agonist and appears to increase serotonin turnover and affect the opioid system. Its elimination half life is approximately 30 to 60 minutes (Krahn, 2003; Owen, 2008), and it has no clear withdrawal syndrome (Owen, 2008). Like sodium oxybate, the mechanism of modafinil is unknown (Ballon & Feifel, 2006). Despite its wake-promoting effects, modafinil's mechanism of action is distinct from that of amphetamines (Ballon & Feifel, 2006). That is, modafinil is not a typical stimulant. In fact, modafinil may activate noradrenergic alpha$_1$ receptors and increase glutamate release in the hippocampal formation and in the thalamus. Modafinil also affects hypocretin function in part at least by activating hypocretin receptors in the lateral hypothalamus and increasing hypocretin release in the perifornical area (Ballon & Feifel, 2006). Like sodium oxybate, modafinil does not appear to be associated with a withdrawal syndrome (Ballon & Feifel, 2006). The half-life of modafinil is approximately 12 to 15 hours (Darwish, Kirby, Hellreigel, & Robertson, 2009; Robertson & Hellriegel, 2003).

In addition to its effects on sleep function, narcolepsy is associated to some degree with compromised cognitive performance. Studies of cognitive functioning in narcolepsy have primarily assessed the effects of daytime sleepiness on memory and attention (Fulda & Schulz, 2001). Indeed, findings by Hood and Bruck (1996) suggest that cognitive impairment in narcolepsy is associated more with the level of drowsiness than with narcolepsy itself. Having subjects rate their level of sleepiness before neuropsychological test administration, Hood and Bruck found that subjects with high arousal (i.e., low sleepiness) performed comparably to healthy controls on automatic attention tasks, while those with low levels of arousal showed attentional impairments, particularly on more complex attention tasks. Similarly, Schulz and Wilde-Frenz (1995) found that tiredness and episodes of sleepiness appear to provide the best explanation for poor cognitive performance in subjects with narcolepsy.

Aside from the well described observations of reduced arousal, other neuropsychological findings in narcolepsy have been less consistent. Several studies examining attention span have not found differences in performance between in narcolepsy compared with controls (Aguirre & Broughton, 1987; Rogers & Rosenberg, 1990; Valley & Broughton, 1981). Other studies, however, show reduced performance in narcolepsy relative to controls on tasks of focused attention (Hood & Bruck, 1996; Pollak, Wagner, Moline, & Monk, 1992), divided attention (Hood & Bruck, 1996), and sustained attention (Mitler, Gujavarty, Sampson, & Browman, 1982). Specific difficulties include poor ability to flexibly allocate attention resources (Rieger, Mayer, & Gauggel, 2003) and maintain vigilance (Fulda & Schultz, 2001).

Given the attentional difficulties associated with narcolepsy, it is not surprising that patients with narcolepsy often report memory difficulties (Naumann, Bellebaum, & Daum, 2006), although findings from studies using objective neuropsychological measures of memory are somewhat variable. For example, Rogers and Rosenberg (1990) found that individuals with narcolepsy have reduced delayed recall of a 30-item word list and diminished performance on a task measuring automatic incidental memory compared to control participants. Similarly, Naumann et al. (2006) found subtle impairments in story recall abilities in subjects with narcolepsy. In contrast, Schulz and Wilde-Frenz (1995) reported that patients with narcolepsy have difficulties only with long-duration, sustained tasks, but not on typical memory encoding and learning tasks. Fulda and Schulz (2001) indicate that conclusive evidence for objective memory impairments in narcolepsy is lacking. The relatively few and heterogeneous findings of memory difficulties in narcolepsy suggest a need for additional studies addressing memory performance and mechanisms underlying memory functioning in this disorder (Naumann & Daum, 2003).

In addition to the comparative lack of research evaluating neuropsychological function in narcolepsy, few studies have examined the effects of stimulant medications on cognitive performance and daily functioning in narcolepsy. Kotterba et al. (2003) measured several neuropsychological domains in narcolepsy subjects, including a measure of accident rates on a driving simulator task, in response to amphetamine intervention. These researchers found that although amphetamine stimulation had very little effect on most of their neuropsychological measures, it significantly reduced rates of concentration lapses and accidents on the driver simulation task. In an early functional imaging study of individuals with narcolepsy and controls on and off amphetamine, Howard et al. (1996) found increased levels of brain activation in the primary auditory and sensory cortices of individuals with narcolepsy with amphetamine treatment but a small decrease in sensory activity in controls.

Few studies have examined the cognitive effects of modafinil in narcolepsy in conjunction with fMRI measures. In one study, self-reported alertness increased after modafinil administration (Ellis et al., 1999), but there were no meaningful differences in the pattern of neural activity between healthy individuals and those with narcolepsy.

No studies to date have specifically examined memory performance and its neural underpinnings in narcolepsy or the effects of modafinil on such performance. Thus, we report the effects of modafinil on performance and neural activity in a 20-year-old woman with narcolepsy compared to normative data during a nonverbal memory task while undergoing functional magnetic resonance imaging (fMRI).

METHOD

fMRI assessment and normative data

Like any other form of neurological or cognitive assessment, fMRI assessments should be interpreted in the context of normative data. This issue is unique to clinical applications of fMRI, as opposed to purely scientific research efforts, as the latter typically relies on group averaging, whereas the former concerns data from single individuals. Recent efforts in clinical fMRI research propose a system of testing protocols, data analysis, and outcome interpretation adapted from standard techniques of cognitive assessment as applied, for example, in contemporary clinical neuropsychology (Allen & Fong, 2008a, 2008b). A critical component of this approach is normative data. The fMRI-adapted face memory test – the f-FMT – used here to test the narcolepsy subject represents one of a series of fMRI-adapted cognitive assessment tests modeled after several of the most commonly used neuropsychological examinations. Importantly, normative data on the f-FMT were obtained from a sample of 38 control subjects and structured into a normative brain activation map representing distributions of expected activation ranges within functionally-defined anatomical regions, against which individual patients might be compared for the purpose of quantitative assessment.

Narcolepsy subject

The subject was a 20-year-old, right-handed Caucasian woman with 15 years of education diagnosed with narcolepsy at age 18 years by a sleep physician and polysomnography. At the time of assessment, she was taking modafinil 200 mg daily, which she had done for the previous 24 months. She was also taking 7.5 grams of sodium oxybate daily, a drug the patient had for the previous 14 months. The subject denied a history of any other neurological or psychiatric conditions, including previous or current substance, alcohol, or nicotine use. Her medical history was remarkable for asthma, for which she took no medications. Other than the modafinil and sodium oxybate, the subject was taking no other medications. The Mental Health Screening Form-III (MHSF-III; Carroll & McGinley, 2000, 2001) showed no current psychiatric difficulties. At the time of her initial fMRI scan, the patient had her first fMRI scan after not taking modafinil for 32 hours. She had taken 4.5 grams of sodium oxybate 20 hours before scanning and 3.0 grams 16 hours before scanning. Sixty-three days later, the patient had a second fMRI scan after taking her usual modafinil dose 4 hours before scanning. As at the first fMRI session, she had taken 4.5 grams of sodium oxybate approximately 20 hours before scanning and 3.0 grams approximately 16 hours before scanning. She was administered the f-FMT task at both fMRI scanning sessions but had a different version of the f-FMT task at each scanning session.

Control participants

Thirty-eight participants (19 male, 19 female) between ages 20 and 39 years (mean = 23.22; *SD* = 4.08) volunteered as control subjects. All participants gave informed consent prior to inclusion in the study by reading a study description and signing a consent form approved by the appropriate institutional review board. Participants received no compensation. All but two subjects (one male, one female) were determined to be dominantly right-handed according to the Edinburg Handedness scale. Thirty-five subjects reported their ethnicity as Caucasian. Two females and one male reported their ethnicities as Hispanic and Asian/Pacific Islander, respectively. All spoke English as their first language. All participants were determined to have no history of neurological impairments (assessed by a screening questionnaire), no significant psychiatric history, and no reported current use of psychotropic medications. High resolution 3D SPGR and T_2 axial FLAIR MRI scans revealed no detectible brain abnormalities in any control

subjects as determined by a neuroradiologist. All subjects had completed at least 1 year of college and were in good academic standing at a university with high admission and continuance standards. All participants consented to release pre-admission records of ACT (or SAT) scores. Analysis of mean scores (with SAT converted to ACT equivalents) revealed overall high performance, with a mean of 30 ($SD = 4.30$) for females, and 29 ($SD = 2.16$) for males, with no significant difference between sexes ($t = 1.38$, $p > 0.1$).

Ninety-six (51 female, 45 male) additional control subjects were recruited from the same population as the fMRI control subjects to participate in a pre-study experiment in which we collected normative data for accuracy on the recognition post-test of the f-FMT.

Functional imaging task – The f-FMT

The f-FMT is a face-encoding episodic-memory test. Face stimuli were 40 color photographs of university students (10 men, 10 women; ages 18–30 years), used with written permission. Each photograph was cropped just above the highest extent of hair and just below the chin and at the sides just beyond the farthest extent of head, hair, or ears. Two versions of the protocol were created, each with 20 faces.

The narcolepsy patient was tested on the f-fMT using identical procedures as those used with control subjects. Prior to entering the scanner, subjects were told that they would be shown 20 different faces and that they should try to memorize each face as best they could and that they would be given a short recognition test after the scanning session in which they would need to 'point out' faces that had been seen in the scanner. At the beginning of each session, a 'please wait prompt' appeared for 8 seconds to allow for T1 relaxation effects. During functional scanning, each photograph was shown twice in split-random order for 3 seconds in series of 5 consecutive stimuli, for an epoch length of 15 seconds. Each test epoch began with a 2-second 'memorize the faces' prompt. Each test epoch alternated with a 13-second 'rest' epoch, in which subjects were instructed to count covertly from 1 to 10. This simple counting task has been empirically supported as an optimal minimal-demand cognitive activity for rest epochs in fMRI experiments in general and for episodic memory tasks specifically (Stark & Squire, 2001). There were a total of 6 test–rest epoch cycles for a session duration of 4 minutes. After functional scanning, 3D FSPGR and T_2 axial FLAIR images were acquired and examined by a neuroradiologist for structural abnormalities.

Recognition post-test

Approximately 30 minutes after administration of the encoding phase of the f-FMT, subjects performed a recognition post-test outside of the scanner. In this post-test, 10 faces from the encoding phase were displayed, one at a time, randomly mixed with 10 new faces. The subjects were instructed to indicate with a verbal 'yes' or 'no' whether the face had been seen in the scanner. A separate version of the post-test was created for each of the two encoding phase versions of the f-FMT.

Data analysis

Identical image acquisition and analysis procedures were used for the patient and control subjects, as described below.

Image acquisition

Functional images were acquired with a 1.5-T GE scanner using an EPIBOLD sequence with the critical parameters TR = 2000 ms; TE = 40 ms; Flip Angle = 90. Images were acquired at 23 contiguous axial locations with a slice thickness of 5 mm, 0 mm interslice gap, with a 3.75 × 3.75 mm in-plane resolution and a 64 × 64 matrix of individual sample points, producing a total of 64 × 64 × 23 voxels for whole brain coverage. Preprocessing procedures included acquisition time realignment, using sinc interpolation, followed by motion correction with EPI distortion unwarping. Acceptable head motion limits were 1 mm translation or 1° rotation displacement. After motion/distortion correction, all functional volumes were spatially normalized and resampled using the Montreal Neurological Institute (MNI) templates implemented in SPM5, and spatially smoothed with an 8 mm FWHM Gaussian kernel in order to increase signal-to-noise ratio and to reduce the effects of moderate inter-subject variability in brain anatomy for group-level random effects (RFX) analysis.

Subject-level analysis

A time-series ANCOVA implemented in SPM5 was used to test each voxel, for each subject, against the null-hypothesis that changes in BOLD signal in that voxel over the duration of the experiment did not significantly correlate with the temporal sequencing of the test and rest epochs. A boxcar waveform convolved with a synthetic hemodynamic response function (HRF) with a 4-second lag-to-peak was used to model task-related activation. The data were high-passed-filtered in time, using a set of discrete cosine basis functions with a cut-off period of 128 seconds, and conditioned for temporal autocorrelations using AR1 correction. For each participant, *t*-values for the contrast test condition versus rest condition, as well as the simple contrast test condition (against an implicit baseline) were computed for each voxel, using the parameter estimates of the ANCOVA. A resulting 3D contrast map from each subject was saved for further group-level random effects (RFX) analysis as well as a corresponding *t*-statistic map from each subject, with a threshold of $p < .05$ FWE corrected (full volume) and a cluster extent threshold of 9 contiguous voxels, which was used for the subject-level functional region analyses.

Group-level analysis

The primary group-level analysis of interest for this study is the functional region analysis, or more specifically, the distribution of values derived from each control subject within each functional region, as it provides the means for a quantitative comparison of any further individuals who are scanned using the f-FMT protocol. Results from the RFX analysis were used only as a supplementary measure to confirm the validity of the mean effects from the functional region analysis, and are not reported in full here.

Subject-specific functional region analysis

A subject-specific functional region analysis using anatomical boundaries adapted from Tsourio-Mazoyer et al. (2002) was performed for the patient and each control participant, using his or her individual brain anatomy with 48 functional brain regions defined for each hemisphere. Specifically, functional region boundaries were identified on each subject's 3D SPGR structural image, which was coregistered to the mean of each subject's functional images prior to statistical analysis. Next, the subject's thresholded *t*-statistic map was smoothed with a 1.5 mm FWHM Gaussian spatial filter, in order to condition extreme *t*-value spikes within peak clusters, and overlain on the parcellated structural image. Each region was then inspected for cluster peaks. If an independent peak was found, the maximum (smoothed) *t*-value was saved as a data point from that subject for that region. When more than one peak cluster was identified within a region, the locations of the peaks were catalogued and, if found consistently across subjects (i.e., $> 30\%$), used to motive further divisions within regional boundaries. However, only those regions (or subregions) with peak clusters present in at least 70% of control subjects were used for further single-subject assessments (although for this study, agreement across subjects in cluster presence/absence exceeded 90%). Additional details regarding this procedure are described in Allen and Fong (2008a). Following *t*-value extraction from each subject, means and standard deviations were computed for each region and used to derive normalized *z*-scores.

The functional region analysis was done primarily for the objectives of the overarching project within which this f-FMT study was embedded, which was to derive normative data suitable for single-case evaluation, as in the current narcolepsy case. However, a second purpose of this custom analysis is that it serves as an additional, complementary measure of reliable brain activation related to the f-FMT, along with the RFX analysis. Specifically, the functional region analysis may be better suited to detect reliable activation of large functional areas (e.g., dorsolateral prefrontal cortex) where subjects may show reliable activation within the boundaries of that functionally-defined region, but with variable foci across subjects.

RESULTS

Control-subjects

Behavioral performance

Performance norms for the post-test recognition task were collected from the 38 fMRI control subjects as well as an additional sample of 96 subjects drawn from the same population as the fMRI control subjects. Subjects were tested on

both versions of the post-test, using a randomly assigned version order, with 1 week between test sessions. Mean correct recognition was 90.1% (SD = 14.8) for version 1, and 89.4% (SD = 13.6) for version 2, with approximately equal rates of false-positives and misses for both versions. Given the clear ceiling effects apparent in the distribution of performance accuracies, standard deviations were estimated using methods given in Alliger, Hanges, and Alexander (1988).

fMRI activation

The subject-specific anatomical region analysis revealed 11 functional regions meeting the reliability criteria for inclusion as a region for further quantitative analysis. The distributions of t-values in each anatomical region were assessed for normality prior to z-score transformation. Anderson–Darling sample-size-adjusted tests for normality determined the distributions of each of the 11 regions to be sufficiently normal, with estimates ranging from moderate (left fusiform gyrus; $A^{2*} = 0.59$, $p = 0.11$) to high (right middle frontal gyrus; $A^{2*} = 0.18$, $p = 0.91$).

The locations of the regions that were identified by our analysis as showing reliable activation peaks across subjects correspond quite well with locations of peak activations identified in previous neuroimaing studies using conventional probability-based anatomical region estimations and group-averaging methods (Buckner, Kelley, & Petersen, 1999; Golby et al., 2001; Haxby et al., 1996; Kelley et al., 1998; McDermott, Buckner, Petersen, Kelley, & Sanders, 1999; Sperling et al., 2001). Similarly, our functional region analysis showed excellent agreement with the outcome of our own RFX analysis at the group level for this sample. Specifically, at a threshold of $p < .001$ FWE full volume corrected (cluster extent threshold = 9), significant activation peaks were found in all 11 functional regions. Likewise, at this threshold, there were no significant peaks outside of the 11 functional regions. These 11 regions fall under 3 functional divisions, including primary memory encoding systems (hippocampus and adjacent medial temporal lobe), executive functioning systems (dorsolateral prefrontal cortex), and ventral visual processing systems (occipital cortex/fusiform gyrus). The 11 regions are listed as column headings in Figure 2, where group means and standard deviations in each column represent summary statistics of the t-values extracted from each control subject in each region.

Narcolepsy patient

Behavioral performance

For Session 1 (no modafinil for 32 hours), the patient scored 60% correct, with equal false positive and miss rates for incorrect responses. According to the performance norms for the f-FMT (M = 89.9%, SD = 14.5), the patient's performance was −2.03 SD below normal. For session 2 (last dose of modafinil 4 hours before scanning), the patient scored 100% correct. According to the performance norms for f-FMT version 2 (M = 89.4, SD = 13.6), her performance was +0.78 SD above normal.

Subjective arousal ratings

During both scanning sessions, the patient was asked to rate her subjective level of sleepiness at various times. Specifically, she was asked to rate on a scale of 1 to 5, how sleepy she felt, with 5 being 'very sleepy' and 1 'not at all sleepy'. Additionally, the patient was asked to report if she had fallen asleep at any time during the scanning session and to report an associated confidence level on a scale of 1 to 5, with 5 reflecting complete confidence in her recollection. For both sessions, the patient rated her sleepiness at 1 ('not at all sleepy') both immediately before and immediately after each scanning session. Likewise, for both sessions she reported that she had not fallen asleep at any time while in the scanner with a confidence level of 5.

fMRI activation

Results from the subject-level ANCOVA analysis of the narcolepsy patient revealed significant peaks of activation in regions largely consistent with the functional region analysis of the control group (as well as with the group-level RFX analysis). Activation results are summarized in Tables 1 and 2 and displayed in Figure 1. The majority of activation peaks for the narcolepsy patient in both sessions fell within the 11 normative functional regions. A few significant peaks were observed outside of the designated functional regions in both sessions. However, these 'spurious' peaks were consistent with the most common spurious peaks in control subjects. That is, they represent areas most often reaching significance in control subjects at the individual subject level, but not with enough consistency to meet criteria for significance on

TABLE 1
Significant activation for the narcolepsy patient 32 hours off modafinil

Brain region	*MNI coordinates*			*t-Score*
Hippocampus/Medial Temporal Lobe				
Right hippocampus	28	−21	−21	12.20
Left hippocampus	−33	−18	−20	7.95
Left amygdala	−24	−2	−18	6.07
Frontal Lobe				
Right middle frontal gyrus	48	17	41	5.01
Right middle frontal gyrus	36	48	17	4.51
Right superior frontal gyrus	15	26	60	4.58
Right inferior frontal gyrus	47	24	32	6.57
Right precentral gyrus	50	−4	45	7.90
Right precentral gyrus	39	−18	59	5.96
Left middle frontal gyrus	−47	13	48	2.64
Left superior frontal gyrus	−17	46	48	5.14
Left superior frontal gyrus	−18	4	72	5.07
Left inferior frontal gyrus	−46	21	19	5.57
Left precentral gyrus	−55	1	41	5.37
Occipital Lobe				
Right fusiform gyrus	35	−76	−4	15.66
Right fusiform gyrus	26	−62	−14	14.35
Right lingual gyrus	21	−98	−11	18.84
Right middle occipital cortex	33	−95	1	15.06
Left fusiform gyrus	−35	−57	−19	14.55
Left lingual gyrus	−31	−84	−16	16.95
Left lingual gyrus	−16	−89	−17	16.41
Left inferior occipital cortex	−38	−77	−17	20.04
Left inferior occipital cortex	−18	−100	−10	16.17
Left middle occipital cortex	−43	−84	−3	13.74
Parietal Lobe				
Right superior parietal lobe	33	−51	64	5.61
Left inferior parietal lobe	−49	−46	56	5.39

Note: Locations of activation peaks are reported in MNI coordinates (x, y, z) at a threshold of $p < .05$, Family Wise Error corrected, with an extent threshold of 9 contiguous voxels.

either the group functional region or RFX analyses. Specifically, these include peaks in the amygdala (session 1 only), as well as the precentral gyrus, the superior frontal gyrus, and the parietal lobe (both sessions).

While the narcolepsy patient's activation may appear generally consistent with controls overall, striking divergences become obvious when quantifying her activation in the context of the group normative data and then comparing deviations from the normative data across sessions. The two regions of most interest for this patient are the hippocampus and frontal lobe, including the medial pre-supplementary motor area (pre-SMA), as these two systems show a remarkable interaction between sessions. In the hippocampus, activation is extremely high in session 1 (32 hours since last dose of modafinil), with maximal extracted *t*-scores of 12.20 and 7.95 in right and left hemispheres, respectively. Referring to the upper panel of Figure 2 (left two columns), these values are +3.50 and +2.82 *SD* above normal. By contrast, in the frontal lobe (Figure 2, upper panel, right 3 columns) activation is on the lower end of normal for the right middle frontal gyrus and completely absent in the pre-SMA.

The activation pattern for session 1 contrasts strongly with that of session 2 (Figure 2, lower panel). In session 2 (4 hours since last dose of modafinil), frontal-lobe activation falls well above normal, with maximal activation in the left middle frontal gyrus, for example, at +2.49 *SD* above the control group mean. Furthermore, hyper-activation of hippocampus is not present in session 2. Instead, *z*-scores for this session fall just above the mean (+0.44 and +0.50 *SD*). In addition, activation throughout the ventral visual processing stream appears closer to normal in session 2 compared to session 1 (compare upper and lower panels of Figure 2, middle 6 columns).

TABLE 2
Significant activation for the narcolepsy patient 4 hours after the last dose of modafinil

Brain region	*MNI coordinates*			*t-Score*
Hippocampus				
Right hippocampus	39	−22	−16	5.25
Left hippocampus	−29	−17	−21	4.01
Frontal Lobe				
Medial pre-supplementary motor area	0	17	49	12.04
Right middle frontal gyrus	40	3	53	9.26
Right middle frontal gyrus	41	30	38	7.71
Right inferior frontal gyrus	51	16	25	8.32
Right inferior frontal gyrus	45	5	26	7.59
Left middle frontal gyrus	−48	15	49	9.61
Left middle frontal gyrus	−32	5	63	9.17
Left middle frontal gyrus	−49	30	38	8.12
Left superior frontal gyrus	−15	10	68	5.52
Left inferior frontal gyrus	−52	23	30	9.50
Left precentral gyrus	−51	10	41	9.38
Occipital Lobe				
Right fusiform gyrus	28	−71	−8	13.51
Right fusiform gyrus	35	−77	−15	8.02
Right lingual gyrus	17	−97	−10	13.73
Right inferior occipital cortex	25	−90	−13	14.03
Right inferior occipital cortex	36	−89	−10	13.28
Right middle occipital cortex	42	−85	10	12.52
Left fusiform gyrus	−33	−58	−13	11.78
Left lingual gyrus	−24	−89	−12	15.17
Left inferior occipital cortex	−31	−68	−8	14.05
Left middle occipital cortex	−36	−83	11	10.96
Parietal Lobe				
Right superior parietal lobe	23	−67	63	5.15
Right intraparietal sulcus	33	−50	43	5.36
Left inferior parietal lobe	−25	−71	43	6.64

Note: Locations of activation peaks are reported in MNI coordinates (x, y, z) at a threshold of $p < .05$, Family Wise Error corrected, with an extent threshold of 9 contiguous voxels.

DISCUSSION

In this report, both behavioral and activation results suggest the hypothesis that modafinil may have normalized f-FMT performance and brain activation in a narcolepsy patient, although this hypothesis requires additional testing in a fully balanced experimental design. In session 1 (32 hours off modafinil), poor performance on the f-FMT recognition post-test ($z = -2.03$) corresponded with a highly atypical activation pattern during memory encoding. The primary feature of this atypical pattern appears to be a marked deficit of activation in frontal systems in contrast to hyperactivation of hippocampus, as well as relatively high activation throughout ventral visual-processing systems. This pattern may suggest hippocampal recruitment in an attempt to compensate for lack of activation in frontal systems during memory encoding, when frontal-lobe functioning appeared compromised. Relatively higher activation in visual processing areas in session 1, with all z-scores greater than 1, suggests additional compensation by these systems as well. In session 2 (4 hours since last does of modafinil) by contrast, flawless performance on the f-FMT recognition post-test ($z = +0.78$) corresponded with a more normalized fMRI activation profile during memory encoding. In contrast to the deficient frontal activation in session 1, activation of frontal areas in session 2 was moderately above normal ($z = +1.26$ to $+2.49$). Likewise, in contrast to hyperactivation of the hippocampus in session 1, hippocampal activation in session 2 fell just above the group mean. However, if this observed hyperactivation does indeed represent an alternative, compensatory, strategy for memory encoding, it would appear to be an inefficient one given the observed deficits in her behavioral performance on the f-FMT.

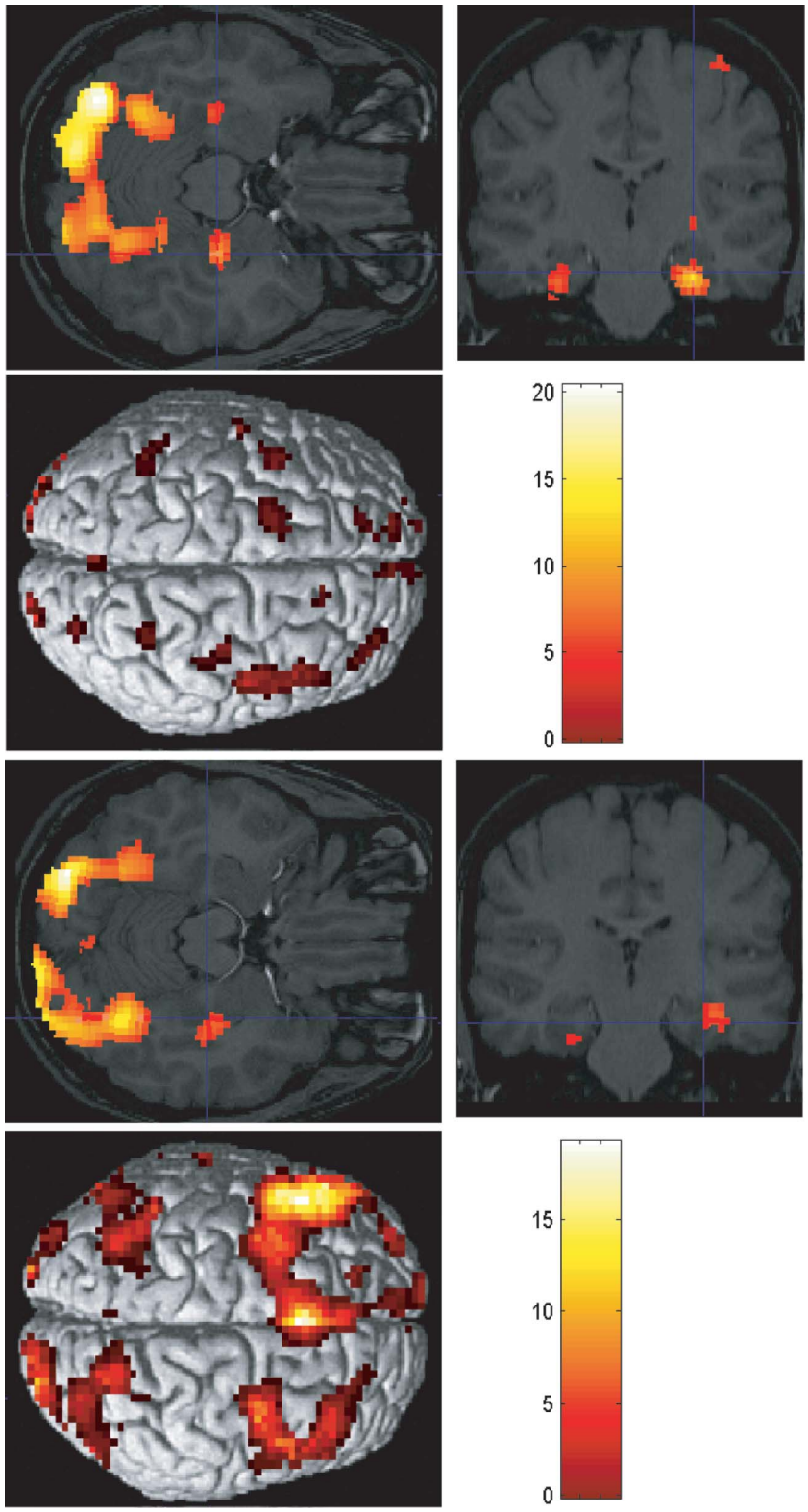
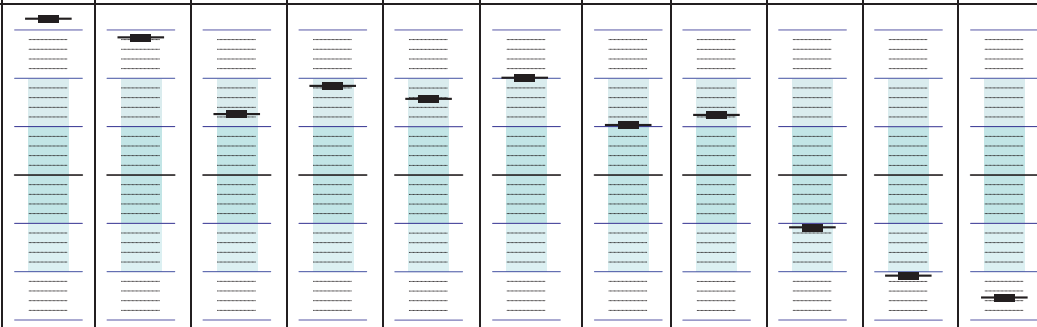


Figure 1. Activation from the session when the narcolepsy patient had been off modafinil for 32 hours (upper panel) and 4 hours since the last dose of modafinil (lower panel) during the encoding phase of the f-FMT face memory test.

Session 1 – 32 hours since last modafinil dose

Region	**Right Hippo-campus**	**Left Hippo-campus**	Right Fusiform Gyrus	Left Fusiform Gyrus	Right Inferior Occipital Gyrus*	Left Inferior Occipital Gyrus*	Right Middle Occipital Gyrus	Left Middle Occipital Gyrus	**Right Middle Frontal Gyrus**	**Left Middle Frontal Gyrus**	**Pre-SMA**
											
Group Mean	4.24	3.16	10.57	8.40	12.99	11.15	11.32	9.20	6.98	5.78	6.77
Group StDev	2.27	1.70	4.04	3.40	3.68	4.38	3.59	3.69	1.80	1.54	2.62
Patient *t* value	**12.20**	**7.95**	15.66	14.55	18.84	20.04	15.06	13.74	**5.01**	**2.64**	**0.00**
Patient *z*-score	**3.50**	**2.82**	1.26	1.81	1.59	2.03	1.04	1.23	**–1.09**	**–2.05**	**–2.59**

Session 2 – 4 hours since last modafinil dose

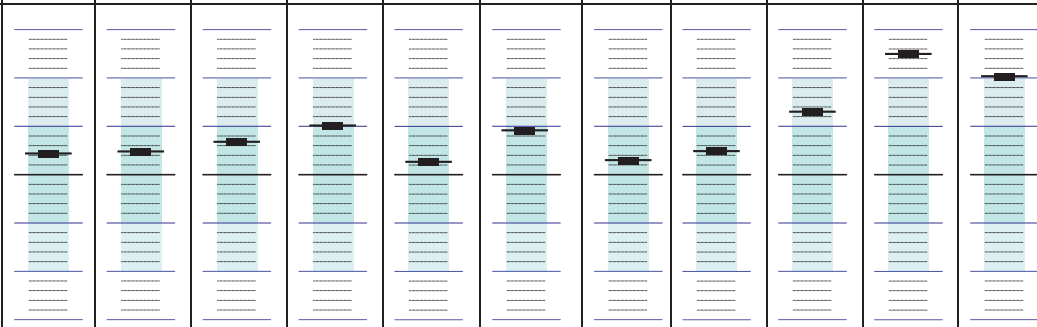
Region	**Right Hippo-campus**	**Left Hippo-campus**	Right Fusiform Gyrus	Left Fusiform Gyrus	Right Inferior Occipital Gyrus*	Left Inferior Occipital Gyrus*	Right Middle Occipital Gyrus	Left Middle Occipital Gyrus	**Right Middle Frontal Gyrus**	**Left Middle Frontal Gyrus**	**Pre-SMA**
											
Group Mean	4.24	3.16	10.57	8.40	12.99	11.15	11.32	9.20	6.98	5.78	6.77
Group StDev	2.27	1.70	4.04	3.40	3.68	4.38	3.59	3.69	1.80	1.54	2.62
Patient *t* value	**5.25**	**4.01**	13.51	11.78	14.03	15.17	12.52	10.96	**9.26**	**9.61**	**12.04**
Patient *z*-score	**0.44**	**0.50**	0.73	1.00	0.28	0.92	0.33	0.48	**1.26**	**2.49**	**2.01**

Figure 2. Normative-based assessment of activation from the narcolepsy patient while performing the f-FMT. Hippocampus is represented in left two columns in bold. Frontal lobe is represented in right three columns in bold. Top panel is from session 1 (32 hours off modafinil), bottom panel is from session 2 (4 hours since last dose of modafinil). SMA, Supplementary Motor Area; *includes lingual gyrus.

At the time of the first fMRI session, the subject had not taken her usual dose of modafinil for 32 hours. As such, it is possible that some of the initial fMRI findings could have been due to a withdrawal from modafinil rather than the lack of modafinil itself. Because modafinil is not associated with a withdrawal syndrome (Ballon & Feifel, 2006), however, such a scenario is unlikely, although given the

half life of modafinil it is likely that the subject still had modafinil in her system. The lack of known withdrawal from sodium oxybate (Owen, 2008) also makes it unlikely that withdrawal from sodium oxybate affected the initial fMRI findings. The short half life of sodium oxybate (Krahn, 2003; Owen, 2008) suggest that by 16 hours after the last dose the subject would have had little remaining sodium oxybate in her system. At the follow-up fMRI scan 63 days later, the only change in the subject's medication status was that she had taken her last dose of modafinil only 4 hours before imaging, instead of 32 hours before imaging as she had done at the first imaging session. Accordingly, she likely had significantly higher blood levels of modafinil at the second fMRI session than at the first. The dose and timing of sodium oxybate administration was the same at both fMRI sessions.

An additional consideration is whether the cognitive and brain-activation effects observed in this patient were a direct result of the action of modafinil on cognitive functioning, or whether instead modafinil played an indirect role by modulating general levels of arousal, which in turn affected cognitive performance. Although the patient reported a similar low degree of 'sleepiness' in both sessions, the methods of this study unfortunately do not provide any further, more objective, sources of evidence to distinguish these alternatives. Simultaneous electroencephalogram or reaction-time measures could be helpful in future studies.

The improvement in the narcolepsy patient's performance on the f-FMT from session 1 to session 2 raises a potential concern about practice effects. While an ABBA design (off modafinil, on modafinil, on modafinil, off modafinil) would have been optimal in this respect, the patient was unavailable for further testing after the two scanning sessions reported here. Several factors, though, argue against an explanation for behavioral and activation differences based on practice effects alone. Most importantly, entirely different sets of faces were used in both sessions. In terms of an explanation based on practice effects, therefore, this leaves only the possibility that perhaps the patient had become more familiar with the testing environment and procedures by the time of session 2. However, that at the time of session 1, the patient had already participated in previous fMRI testing protocols (not reported here) and was thus already familiar with the fMRI testing procedures and environment and was well practiced at performing tasks under those conditions.

Ultimately, however, the AB design of the study is not suited to find unambiguous effects and precludes drawing firm conclusions, because anything happening in the 63 days between the narcolepsy subject's first and second fMRI sessions could have potentially affected the observed changes in the activation patterns. However, the findings in the off-modafinil condition deviate so far from what is expected within the normal range of expected behavior and activation for this young, highly functioning, and otherwise healthy woman that the prospect of a typical confound having caused the effect itself becomes unlikely. Accordingly, we cannot conclude a causal role for modafinil or its associated increase in arousal in the normalization of brain activation and f-FMT performance in this case with the same degree of confidence we could had we used a more systematic study design, but our confidence is still higher than we would have had had we found less extreme difference on and off modafinil. Despite the limitations of the design we used, the results we report can be used to form specific, testable hypotheses about cognitive deficits in narcolepsy and their response to modafinil treatment.

Another limitation related to the AB study-design issue concerns test–retest reliability because the fMRI subjects forming the normed database were only evaluated once with no retest to determine whether changes in activation patterns occurred. The subjects in the behavioral norming procedure were assessed twice, albeit with a shorter period between evaluations of approximately 1 week, compared to the 63-day lag between assessments in the narcolepsy subject.

Reported effects of modafinil on cognitive function vary considerably across studies, depending on specific tasks and populations of interest (for recent reviews, see Ballon & Feifel, 2006; Minzenberg & Carter, 2008). Though relatively few studies have examined the effect of modafinil on recognition memory specifically, the majority of findings to date suggest modest improvements in memory performance (Muller, Steffenhagen, Regenthal, & Bublak, 2004; Turner et al., 2003), particularly in populations with relatively lower cognitive functioning (Randall, Fleck, Shneerson, & File, 2004; Turner, Clark, Dowson, Robbins, & Sahakian 2004). Of specific interest to the current study, Harsh et al. (2006) found significant dose-dependent improvements from modafinil on episodic recognition memory in a large sample of narcolepsy patients. Moreover, practically all studies that

have explored cortical systems associated with modafinil-related cognitive improvements, both in narcolepsy patients (Saletu et al., 2004, 2007) and in other populations (Hunter, Ganesan, Wilkinson, & Spence, 2006; Spence, Green, Wilkinson, & Hunter, 2005; Walsh, Randazzo, Stone, & Schweitzer, 2004) implicate dorsolateral and medial prefrontal cortex as primary targets of increased neural activation.

Although data from the current study contribute to empirical studies on the effects of modafinil on cognitive function, the primary aim of this study is to examine cognitive dysfunction associated with narcolepsy. The in-depth systematic examination of a single case subject presented in this study provides unique data on this issue. Although this study documents a rather severe case of cognitive impairment on a standard face-memory task in a narcolepsy patient, it remains to be seen whether these findings generalize to other narcolepsy patients The comparative activation patterns in this patient suggest that she might rely on an alternative (and apparently inefficient) processing strategy for recognition memory when untreated for narcolepsy. However, it is possible that other narcolepsy patients, particularly those with relatively high life-functioning skills, such as the current patient, might not only show different degrees of impairment on this task, but also differing compensatory strategies. Normative activation data for this task (as well as other common neuropsychological tasks) provide the means to continue comparing individual narcolepsy patients against a healthy sample group in way that preserves important patient-specific details, while also providing a structure for generalizations to emerge at the group level for this class of patients.

In conclusion, the results from this AB trial suggest the hypothesis that modafinil could normalize brain activation and f-FMT performance in some patients with narcolepsy. However, this hypothesis requires testing of further patients with a fully balanced experimental design.

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