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Effects of nicotine withdrawal on verbal working memory and associated brain response

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1. Introduction

Working memory is a cognitive process that enables information to be held and managed online. According to Baddeley's influential model of working memory, an executive component system coordinates modality-specific short-term memory buffering systems (Baddeley, 1992). The phonological loop is the verbal working memory (VWM) subsystem that is used to manage verbal information. Many investigators have employed functional magnetic resonance imaging (fMRI) paradigms, such as the widely used 2-Back task, with great success to examine brain function associated with working memory and its VWM subsystem (Owen et al., 2005).

The effects of nicotine on cognitive function have been debated for decades (e.g., West, 1993; Pritchard and Robinson, 1994; Heishman, 1998; 1999). Cognitive effects are complex, depending on several factors, such as smoking history, number of cigarettes smoked a day, and time since last cigarette (Shiffman et al., 1995; Heishman, 1999; Ernst et al., 2001). It has been demonstrated that administration of nicotine to non-smokers (Heishman, 1998; Bell et al., 1999; Kumari et al., 2003) and smokers in a state of withdrawal improves cognitive performance (Snyder and Henningfield, 1989; Le Houezec et al., 1994; Bell et al., 1999).

Studies of the effects of nicotine withdrawal on a variety of attention, executive, and processing speed measures have yielded mixed results, ranging from worse performance (e.g., Trail Making Test, Symbol Digit Modalities Test, reaction times, and vigilance commission errors, Hatsukami et al., 1989; Computerized Performance Assessment Battery, Snyder et al., 1989; memory search rate, West and Hack, 1991; modified Stroop Interference Test, Gross et al., 1993; Logical Reasoning, Rapid Visual Information Processing Test, Foulds et al., 1996; Continuous Performance Test, Dawkins et al., 2007), no effects (e.g., Sternberg Memory Task, Finger Tapping, long-term word recognition, digit recall, Stroop Interference Test, Foulds et al., 1996), and even better performance (driving simulation, discourse comprehension, Spilich et al., 1992). Results from studies of nicotine withdrawal on working memory, including the 2-Back working memory paradigm, suggest it is associated with worse performance (Pineda et al., 1998; Ernst et al., 2001a; Mendrek et al.,

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2006; Jacobsen, Mencl et al., 2007; Atzori et al., 2008); however some studies have reported no effects (Ernst, et al., 2001b) or nonsignificant trends for worse performance (Xu et al., 2005; 2006).

Functional brain imaging provides valuable complimentary information to the clinical investigator that may improve the sensitivity and reliability of assessments, and provide new methods for construct validation. For instance, brain imaging allows assessment of brain response associated with subjective states, such as craving, and more sensitive assessments of known phenomena. Examples of increased sensitivity are several reports in the clinical literature suggesting that fMRI is able to detect expected brain dysfunction before it is manifested in behavior (e.g., Bookheimer et al., 2000; Sweet et al., 2004). Moreover, functional brain imaging also allows simultaneous examination of related and co-existing neural processes, such as the suspension of default processing during active challenges of other brain systems (Buckner et al., 2008; Sweet et al., 2008; Sweet et al., 2010). Previous studies suggest that increased suppression of the default network activity may be a more sensitive indication of increased task difficulty than changes in the recruited activity in task-related regions (Sweet et al., 2008; Aloia et al., 2009; Sweet et al., 2010). These advances are likely to lead to substantial improvements in our understanding of the cognitive effects of nicotine and nicotine withdrawal.

Only two functional neuroimaging studies have examined the effects of nicotine withdrawal on VWM among healthy adult smokers. In the first study, three levels of n-Back were administered to eight smokers during fMRI and found greater 1-Back activity during abstinence in the dorsolateral left prefrontal cortex (Xu et al., 2005). They found no differences during the 2-Back or 3-Back, and no significant relationships between brain activity and two measures of craving (Schiffman and Jarvik 1976; Tiffany and Drobes, 1991). Reaction times and accuracy assessed outside the scanner tended to be worse during abstinence, but neither was significant. The authors concluded that increased activity during the 1-Back may be a result of abstinence-related inefficiency of neural processing in the dorsolateral prefrontal cortex.

The second study used positron emission tomography (PET) with radiolabelled water ($H_2^{15}O$ utilization) to examine eleven smokers during the 2-Back (Ernst et al., 2001). They did not contrast activation directly to determine withdrawal effects, but found a significant 2-Back-related response in 1485 voxels across four right hemisphere clusters (including Brodmann Areas 32, 46, 40, and 9) during the placebo condition compared to 671 voxels in two right hemisphere clusters (including Brodmann Areas 44 and 46) during the nicotine condition. They did not find significant effects of withdrawal on 2-Back performance. Minnesota Nicotine Withdrawal Scale (MNWS; Shiffman and Gilbert, 2004) ratings of craving were inversely related to activity in the right dorsolateral prefrontal cortex and right inferior parietal lobule, and positively correlated with activity in the right anterior cingulate. None of the relationships between craving and activity were significant during the nicotine condition.

This previous work suggests working memory decline is associated with increased brain activity during withdrawal, and some investigators have concluded that this reflects inefficiency of neural processing (Xu et al., 2005); however previous studies have not examined variability in brain response, or effects on default processing. Increased variability in brain response across regions associated with cognitive challenges may provide a more direct measure of inefficient neural processing. The present study was conducted to better characterize these effects among healthy adult smokers in a placebo-controlled design. Imaging analyses included relative deactivation, contrasts of baseline control conditions for nicotine effects, and assessment and contrasts of the variability of the individual brain

responses. We hypothesized that nicotine withdrawal would be associated with (i) worse performance during the 2-Back task, (ii) more disorganized recruitment of activity in regions known to be associated with 2-Back performance (including premotor, medial prefrontal, and inferior parietal regions), and (iii) further deactivation in the default network.

2. Method

2.1 Participants

Twelve healthy right-handed nicotine dependent smokers (7 women, mean age = 38.67, $sd = 12.91$) were recruited using newspaper advertisements and flyers. Participants smoked an average of 13.42 ($sd = 5.66$) cigarettes per day and reported a mean score of 2.17 ($sd = 5.69$) on the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al., 1991). Participants were excluded from the final study sample if they regularly consumed nicotine in other forms than cigarettes (e.g., cigars, chewing tobacco), if they were diagnosed with current psychiatric or neurological disorders, or if they had any contraindications for MRI (e.g., claustrophobia, specific implants). Two fMRI scans were conducted within three weeks of each other. Sessions were counterbalanced across participants for nicotine administration following overnight abstinence and application of a nicotine or placebo patch prior to the scan. In the placebo condition, participants applied a placebo nicotine patch the morning before one scan. In the nicotine condition, participants applied a Nicoderm CQ (GlaxoSmithKline) nicotine patch dosed to match their smoking behavior (i.e., according to the manufacturers instructions for the first step in smoking cessation) the morning before the scan. Participants were blinded as to whether they were given placebo or nicotine patch prior to the scanning sessions. They applied the supplied patch an average of 3.38 hours ($sd = 0.46$) prior to each scanning session. Participants abstained from cigarette smoking overnight and prior to scanning on both days. This was verified using exhaled carbon monoxide (CO) assessments. Mean CO ppm was 5.25 ($sd = 3.84$) during the nicotine session and 4.33 ($sd = 3.03$) during the placebo session. Prior to scanning participants rated five items from the Craving Measurement Scale (Schiffman et al., 2003) on a scale of 0–100: “I have a desire for a cigarette right now”; “If it were possible I would smoke now”; “All I want right now is a cigarette”; “I have an urge for a cigarette”; “I crave a cigarette right now”. Mood was assessed using the Positive and Negative Affect Scales (PANAS; Watson et al., 1988) immediately before scanning. All participants provided written institutional review board-approved informed consent consistent with the Helsinki Declaration and were compensated \$140.

2.2 Verbal working memory paradigm

To challenge the VWM system, a 2-Back VWM task was alternated with a 0-Back letter vigilance control task and resting baseline within a block design experiment. During the 2-Back series of consonants are presented visually for 500 ms each, with an interstimulus interval of 2500 ms. Participants are asked to make a *yes* or *no* button-press response with their dominant hand following each consonant to indicate whether it is the same as, or different from, the consonant presented two earlier in the series (e.g., w, N, r, N, R, Q, r, q, N, W...). Six 45-second series of 15 consonants were presented. To perform successfully the participant must maintain a demanding cognitive set that includes constant phonemic buffering (i.e., holding consonants in short-term memory), subvocal phonemic rehearsal (repeating consonants without articulating out loud), and executive coordination. Six 0-Back control blocks of 12 consonants each were presented at the same rate preceding each 2-Back block. Participants responded *yes* when a predetermined target consonant (“H” or “h”) appeared and *no* for other consonants using a two button response box. Every consonant block of both tasks contained 33% targets in random locations within each series. Capitalization was randomized throughout to encourage verbal encoding. A 30 second

resting baseline with a crosshair fixation point was presented prior to each 0-Back block. This 2-Back paradigm is widely used in fMRI research, and therefore has the advantage of well-described fMRI brain response including reliable activation of premotor, inferior parietal, and medial prefrontal regions (e.g., Sweet et al., 2008, Owen et al., 2005).

2.3 Image acquisition

Whole-brain echoplanar blood oxygen level dependent (BOLD) fMRI images were acquired in the axial plane using sufficient contiguous slices for whole-brain coverage using a Siemens (Erlangen, Germany) TIM TRIO 3 tesla scanner (TR = 2500 ms, TE = 28 ms, FOV = 192² mm, and matrix size = 64² in 3 mm slices). This procedure yielded 147 whole-brain volumes for each of two six-minute imaging runs, with a spatial resolution of 3 mm³ per voxel. Whole-brain high-resolution (1mm³) T1 images were also acquired immediately prior to BOLD scans for anatomical reference.

2.4 Individual dataset analyses

All fMRI dataset processing and statistical analyses were performed with Analysis of Functional NeuroImages software (AFNI; Cox, 1996). Concatenated 3D+time echoplanar datasets were spatially registered to the fifth volume of the first series to minimize movement artifact. This procedure yields movement correction parameters that are used as covariates in multiple regression analyses to quantify task-related effects. Five participants who exhibited excessive movement during either session were excluded (more than 3mm in any direction during either scan), resulting in a final sample of 12. Multiple regression analyses were used to quantify task-specific activity for each brain voxel of individual datasets. To accomplish this, a regression of the temporal pattern of 2-Back presentation (including hemodynamic transitions modeled as a gamma function), 0-Back control task, and covariates (observed movement, linear drift) was performed using BOLD signal over time as the dependent variable. Resulting individual activation maps reflecting the unique effects of 2-Back and 0-Back compared to the resting baseline were linearly interpolated to volumes with 1 mm³ voxels, coregistered to high-resolution anatomical volumes, and transformed into standard stereotaxic space (Talairach and Tournoux, 1988). A three-dimensional 6 mm Gaussian kernel was applied before group level processing. The resulting individual datasets of brain response to the 2-Back during nicotine and placebo conditions were expressed as voxel-wise t-values, and served as the basic measure of brain activity in group level statistical analyses.

2.5 Group statistical analyses

Region of interest (ROI) analyses were conducted to test regional hypotheses of nicotine/placebo effects on brain function associated with working memory (Poldrack, 2007). Group summary activation maps of significant 2-Back-related brain response during both nicotine administration and during placebo were used to identify ROIs for hypothesis testing. The first step in these analyses was the identification of clusters of significant activation and deactivation that were related to the comparison of the 2-Back task to the 0-Back task in each session. To accomplish this, individual maps of 2-Back effects (relative to the 0-Back task) were compared on a voxel-wise basis to a hypothetical mean of zero using a Student's one-sample t-test. Results were thresholded using a two-tailed $P < 0.001$.

To minimize spatial bias in the empirically defined ROI set toward either of the sessions a conjunctive "or" mask was created. Conjunctive "or" masking is a common method for creating functionally defined ROIs (e.g., Lawrence et al., 2002; Celone et al., 2006; Mitsis et al., 2008; Roberts et al., 2009). It permits hypothesis testing within a meaningfully defined spatial extent and improves statistical power relative to voxel-wise approaches. "Or" masking is advantageous in that it is designed to fairly operationalize valid task-associated

regions of interest within which to test the effects of interest. To create the ROIs, group summary maps for each session were combined such that any brain voxel significantly active in either session was included in a combined group summary map (see Figure 1, Table 1). Only clusters larger than 200 mm³ were used as VWM-specific ROIs in tests of our hypotheses to obtain reliable means of regional brain activity and limit experiment-wise comparisons. Brain activity representing the 2-Back effect was averaged and standard deviations calculated for each ROI of each participant to be used as dependent variables in statistical analyses. Analyses included contrasts across nicotine and placebo conditions to test our hypotheses, and follow-up examination of correlation matrices for descriptive and validation purposes. Correlation analyses included expected relationships to other key measures such as task performance and craving.

3. Results

3.1 Craving and affect

Mean scores on the craving scale were greater during the placebo condition (300, *sd* = 146) compared to the nicotine condition (246, *sd* = 183); however, this difference was classified as a trend in the expected direction ($t = 1.528$, $P = 0.078$, $d = 0.321$). Mean negative affect scores from the PANAS increased significantly ($t = 2.482$, $P = 0.015$, $d = 0.813$) during the placebo condition (13.50, *sd* = 3.83) relative to the nicotine condition (11.09, *sd* = 1.72). Mean positive affect did not significantly differ ($t = -1.268$, $P = 0.231$, $d = -0.084$) between the placebo condition (29.48, *sd* = 8.44) and nicotine conditions (30.14, *sd* = 7.30).

3.2 Behavioral performance

Mean percent correct responses on the 2-Back were significantly lower than the 0-Back during both conditions (nicotine: $t = -7.387$, $P < 0.001$, $d = -4.524$; placebo: $t = -6.044$, $P < 0.001$, $d = -2.108$); however, there were no significant differences ($t = -0.367$, $P = 0.721$, $d = -0.156$) between 2-Back accuracy during nicotine (mean = 72.42, *sd* = 7.56) and placebo (mean = 73.92, *sd* = 11.27) conditions. Accuracy on the 0-Back did not differ between nicotine (mean = 98.00, *sd* = 2.70) and placebo (mean = 94.83, *sd* = 8.36) conditions ($t = -1.318$, $P = 0.214$, $d = 0.510$), nor did commission errors during 0-Back ($t = -1.123$, $P = 0.285$, $d = -0.486$) or 2-Back ($t = 1.463$, $P = 0.171$, $d = 0.394$).

Analyses of mean reaction times revealed the same pattern in which significant differences were observed only in the comparison between 2-Back and 0-Back (nicotine: $t = -4.576$, $P = 0.001$, $d = -1.682$; placebo: $t = -3.499$, $P = 0.005$, $d = -1.188$). Mean 2-Back reaction time did not differ between nicotine (mean = 839 ms, *sd* = 179) and placebo (mean = 867 ms, *sd* = 229) conditions ($t = 0.658$, $p = 0.524$, $d =$). Likewise, 0-Back reaction time differences were not significant between nicotine (mean = 617 ms, *sd* = 53) and placebo (mean = 653, *sd* = 113) conditions ($t = -1.142$, $P = 0.278$, $d = -0.408$).

3.3 Group summary activity

Successful performance of the 2-Back (i.e., above chance) was associated with significant brain activation in 14 brain regions and significant relative deactivation in five brain regions (see Figure 1 and Table 1). There was a remarkable difference in the pattern of brain response during the two sessions. Although these qualitative findings suggest differences by session, direct ROI contrasts were conducted to determine if these differences were significant in comparison to each other.

3.4 ROI analyses of verbal working memory

Results of the ROI analyses are presented in Table 2. Thirteen out of 14 active regions exhibited less activity in the placebo condition; however, only one of these contrasts was

classified as a statistical trend (right inferior temporal gyrus), and none were significant. In eight out of 14 ROIs, significant inverse correlations were observed between reported cigarette craving and the magnitude of brain response during the placebo condition. Follow-up correlation analyses between craving during placebo and the (albeit non-significant) activation differences between placebo and nicotine conditions were significant in all eight ROIs ($P < 0.05$). Thus, the decline in activity from nicotine to placebo conditions was significantly attributed to increased craving during the placebo condition in eight ROIs. Similar trends ($P < 0.10$) were observed in three additional ROIs (see Table 2). Relationships with craving were not significant in the remaining three ROIs ($P > 0.10$). Variability of individual brain responses (standard deviations associated with mean task-related response within each ROI) differed significantly between nicotine and placebo conditions in nine out of 14 active regions, with trends in three of the five remaining ROIs. Individual variability was greater during the placebo condition in all regions. No significant relationship was observed between craving and brain activity during the nicotine condition.

In three out of five deactivated regions (left medial frontal gyrus and left and right temporal pole), significantly greater deactivation was observed during the placebo session (see Table 2). Craving during the placebo condition was not significantly related to deactivation levels during the placebo condition. However, correlations between craving and brain activity during the placebo condition revealed strong inverse relationships (Table 2). Significant positive relationships were observed between craving and deactivation during the nicotine condition in three out of five ROIs, such that less craving was associated with greater deactivation. Variability of individual brain responses differed significantly between nicotine and placebo conditions only in the right paracentral lobule (see Table 2). Consistent with the active regions, individual variability in deactivated regions was greater during the placebo condition.

Although successful performance of the 2-Back was associated with the pattern of brain response shown in Figure 1 and Table 1, accuracy and reaction time were not significantly related to craving levels, smoking severity (i.e., cigarettes smoked per day), or the magnitude of response in any ROIs ($P > 0.05$).

To examine the possibility of confounding baseline differences, brain response to the 0-Back relative to the resting baseline was contrasted by nicotine condition in all 19 ROIs using the same methods. These contrasts revealed only one significant difference between nicotine conditions. The paracentral lobule response to the 0-Back control task was significantly lower (more deactivation) during the nicotine condition than the placebo condition ($t = 2.837$, $P = 0.016$, $d = 0.880$). It is notable that this is the only deactivated region that exhibited greater deactivation during the *nicotine* condition. Combined with a lack of nicotine-related performance differences during the 0-Back, this suggests that the observed effects of withdrawal on 2-Back related deactivation were not confounded by differences during the 0-Back control task in any region but the paracentral lobule.

4. Discussion

Our findings suggest that nicotine withdrawal has strong effects on the brain response to a demanding working memory task. Differences were observed between the pattern of brain response during the nicotine condition, which was consistent with previous fMRI studies of the 2-Back (Owen et al., 2005; Sweet et al., 2008), and the response during the placebo condition, which was not (see Figure 1). Direct contrasts of brain activity demonstrated during the two sessions revealed differences in the magnitude and variability of responses in regions associated with successful performance of the working memory challenge. In ROIs that exhibited an activation response to the task, increases in variability (12/14 ROIs) and

declines in magnitude (13/14 ROIs) were observed. In three out of the five regions that exhibited a significant deactivation response to the working memory challenge (left medial frontal gyrus and the left and right anterior temporal lobe), further deactivation was observed during nicotine withdrawal. Increased variability during withdrawal was observed in only one region of deactivation (right paracentral lobule).

Relationships to craving levels differed between active and deactive regions. Craving during withdrawal was significantly positively related to the brain response in the majority of actively recruited regions and not significantly related to response in the deactivated regions. That is, more craving was related to less activity. By contrast craving during the nicotine condition was significantly positively related to the majority of deactivated regions and none of the active regions. That is, more craving was related to less deactivation. One possible explanation for this pattern is that higher craving levels led to lower magnitude of task-related activation and deactivation due to greater variability of the responses, which may serve as a possible marker of inefficient processing.

Despite the findings of significantly greater deactivation during placebo in regions of task-related deactivation, we found no significant differences in the regions of task-elicited recruitment. One possible reason for this is the increased variability in predominantly active regions. These findings are consistent with the findings of Xu et al., (2005) who found no significant withdrawal effects on magnitude of brain activity during the 2-Back and suggest a possible difference from the findings of Ernst et al., (2001b), who found larger *volumes* of significant recruitment during withdrawal. Deactivations and individual variability were not reported in these studies.

There were several differences between this fMRI study and the PET investigation by Ernst and colleagues (Ernst, et al., 2001b) that may account for different brain imaging findings. A major difference was that they quantified volumes of significant activity and did not directly compare nicotine and placebo conditions. Also, baseline levels of activity during the 0-Back were not contrasted in the Ernst et al. study to confirm that it did not vary by nicotine condition. Their sample smoked an average of 33.9 cigarettes per day, which is approximately 2.5 times the rate in our sample. Likewise, their FTND severity (6.9) was over three times greater than our sample. Therefore, differences in the direction of nicotine effects compared to previous functional neuroimaging studies of healthy adult smokers may be attributed to the mild severity of nicotine dependence in our group. It is interesting that our finding of relatively increased brain activity in response to nicotine administration is more consistent with the patterns observed among nonsmokers (Kumari et al., 2003) than smokers (Ernst et al., 2001b).

Greater deactivation response to withdrawal in the medial frontal gyri, regions frequently reported to be deactivated during the 2-Back, suggests that the default mode network may be affected. The medial frontal cortices are one of the core regions of the default network, which is most active at rest and suspends activity when people engage in active cognitive processes (Buckner et al., 2008). It has been demonstrated that regions associated with the default network, including the medial frontal cortices deactivate during the 2-Back task, and further deactivate as task demands increase (Sweet et al., 2008). Therefore, it is likely that further suspension of medial frontal activity relative to the 0-Back baseline represents further suspension of the brain's default baseline processing, reflecting a shift in attentional focus in response to increased craving. Although it is possible that an active process attenuates default processing, we did not find evidence for this. Therefore, we conclude that baseline neural processing unrelated to the task demands are relatively abandoned as attentional focus is maintained elsewhere. Accuracy and reaction times were not related to medial prefrontal activity; however, commission rates significantly declined across the

group in the placebo condition with greater deactivation in this region ($r = 0.59$, $P = 0.042$). Although anterior temporal regions have been included as part of the default network, withdrawal effects on the anterior temporal lobes may also have been related to an emotional response associated with observed changes in craving and affect.

Limitations to this study include the mild nicotine dependence reported by our sample. We attribute our observation of a non-significant trend for greater craving during the placebo condition to the mild levels of dependence observed in our sample and to the fact that nicotine patches are typically used in nicotine cessation. Since we used recommended manufacturers doses for the first phase of smoking cessation during the nicotine condition, it is possible that the smokers were experiencing some mild withdrawal symptoms in the nicotine condition. Another limitation is the possibility of increased experiment-wise error. There were inferential contrasts of mean task-related effect and the variability of this effect, as well as descriptive correlational analyses for each ROI. We have included effect sizes to supplement p-values to better inform the reader in the interpretation of effects across multiple comparisons.

In sum, we found that overnight abstinence in a sample mild cigarette smokers was associated with increased variability in brain response to a difficult working memory challenge and relatively greater suppression of regions associated with the default network. The magnitude of task-related activation was significantly inversely related to craving in the majority of regions during the placebo condition. Results support previous literature that suggests inefficient cognitive processing among smokers during nicotine abstinence.

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Figure 1. Response to the 2-Back as a function of nicotine condition

Notes: Blue clusters are associated with the nicotine condition and red clusters are associated with the placebo condition. Numbers correspond to labels in the tables, with negative numbers referring to clusters of deactivation.

Table 1

Regions of significant response to the 2-Back.

Rank and Label		Size mm ³	Center Coordinates		
Activation			x	y	z
1	Left inferior Parietal Lobule	2280	36	57	37
2	Right Inferior Parietal Lobule	1857	-42	50	33
3	Left Cerebellum	1461	24	65	-27
4	Left Middle/Inferior Temporal Gyrus	1385	50	46	-09
5	Righ inferior Temporal Gyrus	785	-58	25	-17
6	Left Middle Frontal Gyrus	781	32	05	46
7	Right Precuneus	717	-28	68	38
8	Right Middle Frontal Gyrus	623	-42	-17	36
9	Right Cerebellum	595	-33	59	-26
10	Left Anterior Insula	494	38	-13	13
11	Right Anterior Insula	450	-33	-19	09
12	Right Thalamus	404	-04	20	17
13	Left Caudate Tail	389	15	23	23
14	Right Cerebellum	361	-11	69	-27
Deactivation					
-1	Left Medial Frontal Gyrus	2959	03	-53	-02
-2	Left Anterior Cingulate Cortex	1876	02	-20	-03
3	Right Paracentral Lobule	344	-04	17	43

Rank and Label	Size mm ³	Center Coordinates		
		x	y	z
-4 Left Temporal Pole	317	49	-08	-24
-5 Right Temporal Pole	208	-28	-15	-20

Note: Rank numbers correspond to labels in Figure 1.

Table 2

Relationship to craving and contrasts of withdrawal effects.

Rank and Label	Contrast of Mean				Relation to Craving				Contrast of Individual Variability			
	Nicotine Effects		Off		On		Off		On		Off	
	Off	On	t	p	d	r	p	r	p	On	t	p
Activation												
1 Left inferior Parietal Lobule	0.55	0.68	-0.61	0.55	-0.24	-0.81	<0.01	-0.39	0.22	1.05	0.84	3.11 0.01 1.31
2 Right Inferior Parietal Lobule	0.67	0.75	-0.28	0.78	-0.12	-0.73	<0.01	0.34	0.29	1.07	0.80	2.49 0.03 1.03
3 Left Cerebellum	0.57	0.68	-0.58	0.58	0.01	-0.74	<0.01	0.22	0.49	1.04	0.79	2.42 0.03 0.97
4 Left Middle/Inferior Temporal Gyrus	0.22	0.55	-1.22	0.25	-0.53	-0.77	<0.01	0.44	0.15	0.99	0.80	2.88 0.02 1.00
5 Right inferior Temporal Gyrus	0.22	0.53	-2.13	0.06	-0.92	-0.53	0.08	-0.06	0.85	0.87	0.71	1.92 0.08 0.73
6 Left Middle Frontal Gyrus	0.52	0.63	-0.57	0.58	-0.22	-0.75	<0.01	-0.06	0.84	0.88	0.73	2.21 0.05 0.79
7 Right Precuneus	0.96	0.89	0.25	0.81	0.09	-0.38	0.23	-0.06	0.84	1.11	0.85	3.29 <0.01 0.93
8 Right Middle Frontal Gyrus	0.56	0.67	-0.34	0.74	-0.12	-0.42	0.17	-0.24	0.46	0.90	0.74	2.13 0.06 0.65
9 Right Cerebellum	0.60	0.84	-1.38	0.19	-0.46	-0.04	0.91	0.02	0.95	1.06	0.79	2.62 0.02 0.87
10 Left Anterior Insula	0.43	0.62	-0.85	0.41	-0.30	-0.55	0.06	0.16	0.63	0.79	0.75	0.38 0.71 0.19
11 Right Anterior Insula	0.81	1.13	-1.42	0.19	-0.41	-0.56	0.06	-0.29	0.35	0.78	0.73	1.13 0.28 0.23
12 Right Thalamus	0.19	0.53	-1.60	0.14	-0.58	-0.70	0.01	0.30	0.34	0.90	0.66	1.98 0.07 0.81
13 Left Caudate Tail	0.27	0.48	-0.86	0.41	-1.57	-0.65	0.02	0.10	0.76	0.84	0.63	2.19 0.05 0.89
14 Right Cerebellum	0.29	0.61	-1.10	0.30	-0.49	-0.64	0.03	0.28	0.38	0.98	0.71	2.91 0.01 1.17
Deactivation												
-1 Left Medial Frontal Gyrus	-1.22	-0.57	-3.15	<0.01	-1.15	-0.14	0.67	0.44	0.15	1.29	1.23	0.47 0.65 0.20
-2 Left Anterior Cingulate Cortex	-0.96	-0.71	-1.33	0.21	-0.47	0.13	0.69	0.60	0.04	1.09	0.93	1.36 0.20 0.57
-3 Right Paracentral Lobule	-0.40	-0.73	1.08	0.30	0.43	-0.14	0.66	0.70	0.01	0.88	0.70	2.35 0.04 0.79

Rank and Label	Contrast of Mean				Relation to Craving				Contrast of Individual Variability			
	Nicotine Effects		Off		On		Off		On		Off	
	On	Off	t	p	d	r	p	r	p	t	p	d
-4 Left Temporal Pole	-0.79	-0.20	-2.97	0.01	-1.27	-0.41	0.19	0.49	0.11	0.76	0.73	-0.12
-5 Right Temporal Pole	-0.82	-0.23	-3.68	<0.01	-1.49	-0.27	0.40	0.58	0.05	0.83	0.72	0.13

Note: Rank numbers correspond to labels in Figure 1. On = Nicotine, Off = Placebo.