Greater BOLD activity but more efficient connectivity is associated with better cognitive performance within a sample of nicotine-deprived smokers

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ABSTRACT

The first few days of an attempt to quit smoking are marked by impairments in cognitive domains, such as working memory and attention. These cognitive impairments have been linked to increased risk for relapse. Little is known about individual differences in the cognitive impairments that accompany deprivation or the neural processing reflected in those differences. In order to address this knowledge gap, we collected functional magnetic resonance imaging (fMRI) data from 118 nicotine-deprived smokers while they performed a verbal *n*-back task. We predicted better performance would be associated with more efficient patterns of brain activation and effective connectivity. Results indicated that performance was positively related to load-related activation in the left dorsolateral prefrontal cortex and the left lateral premotor cortex. Additionally, effective connectivity patterns differed as a function of performance, with more accurate participants having simpler, more parsimonious network models than did worse participants. Cognitive efficiency is typically thought of as less neural activation for equal or superior behavioral performance. Taken together, findings suggest cognitive efficiency should not be viewed solely in terms of amount of activation but that both the magnitude of activation within and degree of covariation between task-critical structures must be considered. This research highlights the benefit of combining traditional fMRI analysis with newer methods for modeling brain connectivity. These results suggest a possible role for indices of network functioning in assessing relapse risk in quitting smokers as well as offer potentially useful targets for novel intervention strategies.

Keywords   Addiction, connectivity, fMRI, individual differences, smoking, working memory.

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INTRODUCTION

For quitting smokers, the beginning of a cessation attempt is often the hardest. Hughes, Keely & Naud (2004) found that most relapse occurred within the first 8 days of a quit attempt. In a different sample, 50% of those who eventually relapsed did so within the first 24 hours (Allen *et al.* 2008). During the initial hours and days after quitting, abstinent smokers experience reduced cognitive functioning (Parrott *et al.* 1996; Hughes 2007). In particular, working memory and attention are profoundly affected by nicotine deprivation (e.g. Shiffman *et al.* 2006; Loughead *et al.* 2009; Sweet *et al.* 2010). For example, Mendrek *et al.* (2006) reported that abstinent smokers made more errors and took longer to respond than non-abstinent smokers in a 2-back version of the *n*-back working memory task. The deleterious effects of nicotine deprivation on cognition likely influence relapse risk. Consistent with this view, Patterson *et al.* (2010) found that slower reaction time during an *n*-back task (indicative of poorer working memory functioning) following 3 days of nicotine abstinence predicted faster return to smoking during a subsequent period in which participants were paid to remain abstinent.

Finn's (2002) cognitive-motivational theory offers a useful model for understanding how attention and working memory influence smoking behavior and relapse. Persons with greater capacity are better able to preferentially attend to less salient, future consequences of decisions over more salient, immediately rewarding

choices. Also, more capacity should facilitate greater mental manipulation of information, thus allowing one to reflect and deliberate on one's choices. Finally, greater capacity should also enable extended deliberations and increased dual-tasking ability (e.g. recalling abstinence goals while tempted).

Collectively, studies indicate that smokers have attenuated attentional control and working memory during the initial hours of a quit attempt and that this reduced functioning may play an important role in contributing to relapse (Hughes 2007; Allen *et al.* 2008; Patterson *et al.* 2010; see also Goldstein & Volkow 2011). It is therefore critical to understand how cognition functions in these persons during this risky time period. In particular, characterizing individual variability in cognition while abstinent may be helpful in understanding differences in susceptibility to relapse. Neuro-imaging is uniquely poised to address this issue because it allows researchers to examine the neural dynamics supporting cognitive processes, thereby providing insight into the mechanisms that underlie disparities in performance across individuals.

Here, we used fMRI to examine variability in cognitive performance and patterns of brain activation among nicotine-deprived smokers during the performance of an *n*-back working memory task. The *n*-back is ideal for exploring cognitive functioning because it produces robust and consistent patterns of brain activation (Owen *et al.* 2005). Furthermore, the *n*-back allows one to vary memory load. This provides a high-load/ minimal-load contrast, which presumably closely resembles the task of a quitting smoker who must increasingly utilize cognitive processes in order to remain abstinent during tempting episodes. Accordingly, individual differences in one's ability to engage these resources during the *n*-back task may relate to one's ability to manage the urge to smoke.

Several studies have observed a paradoxical relationship between brain activation and effective use of cognitive processes, such that successful processing is related to attenuated neural activity (e.g. Nakamura, Hillary & Biswal 2009), perhaps because higher performing participants utilize cognitive resources more efficiently (e.g. Jaeggi *et al.* 2007). These patterns are broadly consistent with research demonstrating practice-related reductions in brain activation following extensive performance of various cognitive tasks (e.g. Landau *et al.* 2004; Chein & Schneider 2005). Taken together, these lines of research suggest that level of performance is inversely related to the magnitude of task-induced activation in areas of the brain supporting domain-general processes (e.g. attention and working memory). Accordingly, we predicted that *n*-back performance and brain activation would be negatively related among deprived smokers.

Furthermore, we hypothesized that examining the nature of associations *between* areas of the brain linked to attention and working memory—above and beyond assessing differences in the mean activation level within brain regions in isolation—would be particularly informative regarding the neurocognitive mechanisms that underlie differences in cognitive performance (e.g. McIntosh 2000; Sporns 2011). There is some evidence that inter-individual variability in cognitive performance is related to the efficiency of functional brain networks (operationalized as the number and strength of connections between brain areas). For instance, on a speeded processing task, slower participants exhibited more inter-regional influences than faster participants (Rypma *et al.* 2006). This was interpreted as indicating that slower participants had fewer direct connections between areas supporting cognitive processing and thus more indirect (and total overall) connections.

A primary goal of the current study was to test the hypothesis that similar network-related differences underlie variability in cognitive task performance among nicotine-deprived smokers. To test this prediction, we explored the association between behavioral performance and effective connectivity (Friston 1994, 2011) during the *n*-back task using unified structural equation modeling (uSEM; Kim *et al.* 2007; Gates *et al.* 2010). uSEM combines traditional structural equation modeling and vector auto-regression to arrive at more accurate structural models (see Supporting Information Appendix S1 for more information about uSEM).

Model identification was conducted using Group Iterative Multiple Model Estimation (GIMME; Gates & Molenaar 2012), a state-of-the-art method for arriving at reliable individual-level connectivity maps by using shared information across the sample. In a first step, GIMME arrives at a valid group-level map. For this study, the most important feature of GIMME surrounds its recovery of individual-level networks in a second step. GIMME improves upon individual-level approaches by using the group-level connections as a basis for semi-confirmatory search. GIMME has demonstrated more accurate recovery of individual-level networks than most other popular methods (see Gates & Molenaar 2012; for more information about our rationale and implementation of GIMME, see Supporting Information Appendix S1).

In summary, we sought to better delineate individual differences in the cortical networks underlying cognitive functioning among nicotine-deprived smokers. We predicted that better performance would be associated with more efficient patterns of task-related brain activity. Specifically, we hypothesized that brain network complexity would be negatively related to task performance. Participants were abstinent from nicotine for 12 hours prior to

the imaging visit. As roughly half of all relapse occurs within 24-hours of a quit attempt (Allen *et al.* 2008), this manipulation offered as a useful model of cognitive functioning during a high-risk period during smoking cessation.

METHODS

Participants

Participants were drawn from two fMRI studies. Study 1 (Wilson, Sayette & Fiez 2012a) examined the effects of quitting motivation and smoking opportunity on cue-elicited neural responses; the study included both males and females and smokers who were and who were not motivated to quit smoking. Study 2 (Wilson, Sayette, & Fiez 2012b) examined neural responses associated with different strategies for coping with a smoking cue coupled with the opportunity to smoke; the study included male smokers who were motivated to quit smoking. For both, participants had to report smoking an average of 15–40 cigarettes/day for the past 24 months and had to be right-handed.

One hundred eighteen participants (77 from study 1 and 41 from study 2) were included in the present analyses. Sample characteristics are reported in Table 1. As expected, the gender distribution of the samples selected from study 1 and study 2 differed significantly, $\chi^2(1, N = 118) = 22.4$; $P < 0.001$. Additionally, the sample from study 2 was older [$t(116) = 2.04$, $P = 0.04$] and had a lower postdeprivation carbon monoxide (CO) reading [$t(116) = 2.63$, $P = 0.01$] than the sample from study 1, but mean differences in these variables were modest (see Table 1). Samples did not differ in baseline CO, cigarettes/day, years of education, level of nicotine dependence [as assessed with the Fagerstrom Test for Nicotine Dependence (FTND); Heatherton, Kozlowski, Frecker, & Fagerstrom 1991], prescan self-reported craving (assessed using a single-item 0–100 scale), or primary behavioral or neural experimental measures ($Ps > 0.06$). Smokers who were motivated to quit did not differ from non-motivated smokers in *n*-back performance or in primary neural measures ($Ps > 0.37$). Informed consent was obtained from all participants, and procedures were approved by the local Institutional Review Board.

Baseline measures

During a baseline assessment, information regarding demographics and smoking patterns were assessed with standard forms (Sayette *et al.* 2001). Participants also completed questionnaires and tasks assessing several constructs, including level of nicotine dependence, smoking abstinence self-efficacy, trait self-control, affect and socially desirable responding. These data are not a focus of the present study (see Wilson *et al.* 2012a).

N-back task

Participants performed several blocks of a verbal *n*-back task while fMRI data were acquired. During each 36-second block, a randomly selected set of 12 letters were presented individually (500 ms stimulus duration, 2500 ms interstimulus interval). Participants performed two versions of the task that varied in working memory load: a control version of the task with minimal memory requirements (0-back), during which participants were instructed to press a button with their right index finger if the letter 'X' appeared; and a version with comparatively high memory load (3-back), during which participants were instructed to similarly press a button if the currently presented letter matched the letter presented three items previously. See Supporting Information Appendix S1 for additional task details.

Procedure

Participants completed two sessions, which are described in detail elsewhere (Wilson *et al.* 2012a,b). Briefly, for both studies, those eligible based upon a telephone screening were scheduled for an initial baseline session during which questionnaires and tasks were administered. For study 2, participants were trained to use one of

Table 1 Sample characteristics.

	Full sample (n = 118)	*Study 1* (n = 77)	*Study 2* (n = 41)
Percent male	74	60	100
Percent quitting-motivated	69	52	100
Mean age (SD)	30.8 (7.9)	29.7 (7.3)	32.8 (8.7)
Mean years of formal education (SD)	12.8 (2.1)	12.8 (2.4)	12.8 (1.6)
Mean cigarettes/day (SD)	19.8 (4.9)	19.7 (5.2)	20.1 (4.3)
Mean FTND score (SD)	4.9 (1.6)	4.9 (1.6)	4.6 (1.6)
Pre-scan urge to smoke (0–100) (SD)	63.9 (29.7)	64.8 (25.8)	62.3 (30.7)
Baseline CO (SD)	29.7 (12.6)	28.7 (12.9)	31.7 (11.9)
Experimental CO (SD)	11.9 (5.3)	11.1 (4.9)	13.7 (5.8)

two strategies for coping with smoking cue exposure. Participants then were scheduled for the experimental session. They were instructed to abstain from smoking and from using any nicotine-containing products for at least 12-hours prior to the experiment and that compliance would be verified with a CO sample.

Upon arrival for the experimental session, which was held within 2 weeks of the baseline session, participants reported the last time they smoked, and CO was measured to check compliance with deprivation instructions. Participants needed a CO level that was at least 50% lower than their baseline, a cutoff based upon research using similar samples and procedures (e.g. Sayette *et al.* 2008). Participants rated their urge to smoke and were informed about whether or not they would be permitted to smoke during the study. Importantly, participants told that they could and could not smoke did not differ in self-reported urge to smoke, *n*-back performance, brain activation, or our primary measure of neural efficiency ($Ps > 0.09$). After the collection of anatomical images, participants completed the verbal *n*-back task. Subsequently, participants completed a cigarette cue exposure task, the results from which are reported elsewhere (Wilson *et al.* 2012a,b). Following the cue exposure task, participants were removed from the scanner for a brief break (and were permitted to smoke, if applicable), after which they completed post-task questionnaires and were debriefed.

fMRI methods

Scanning was conducted using a 3-Tesla Siemens Allegra magnet (Siemens Corporation, New York, NY, USA). Prior to functional scanning, a 40 slice oblique-axial anatomical series ($3.125 \times 3.125 \times 3.0$ mm voxels) was obtained using a T2-weighted pulse sequence. Additionally, a high-resolution ($1 \times 1 \times 1$ mm voxels), three-dimensional structural volume was collected using an MPRAGE sequence. Next, functional images were acquired in the same plane as the 40-slice anatomical series with coverage limited to the 38 center slices using a one-shot EPI pulse sequence [repetition time (TR) = 2000 ms, echo time = 25 ms, field of view = 20 cm, flip angle = 79°]. Several preprocessing steps were employed to correct for artifacts and to account for individual differences in anatomy prior to analyzing fMRI data (see Supporting Information Appendix S1 for details).

fMRI data analysis

Region of interest (ROI) selection

The primary aim of analysis was to examine the relationship between behavioral performance and patterns of activation among brain regions sensitive to increasing demands during *n*-back task performance. In order to identify regions exhibiting load-dependent increases in

activation, a two-level random-effects general linear model (GLM) was implemented on a voxel-wise basis using Analysis of Functional NeuroImages (AFNI) 3dDeconvolve (Cox 1996). First, predictors for each *n*-back condition were entered into a GLM to obtain parameter estimates (i.e. beta coefficients) for each participant. The resulting beta weight estimates were entered into a second-level paired *t*-test in order to generate regions exhibiting a main effect of memory load (i.e. 3-back versus 0-back). The voxel-wise significance threshold was set at $P < 1 \times 10^{-18}$ for this contrast, with a spatial extent threshold of 10 contiguous voxels. [Based upon Monte Carlo simulations conducted using AFNI AlphaSim (Cox 1996), it was determined that this yielded a corrected map-wise false positive rate of $P < 0.001$.] Data from regions identified in this contrast were extracted for inclusion in subsequent analysis, described below.

Examining performance-related differences in activation within independent ROIs

To examine the relationship between behavioral performance and load-dependent activation during the *n*-back task, additional analyses were conducted on data extracted from the ROIs identified using the procedure described above. Specifically, linear regression was conducted for each ROI, with mean load-related change in activation for significant voxels in the region as the independent measure and 3-back performance as the dependent factor. As urge to smoke was unrelated to brain activation ($Ps > 0.05$), it was not included as a covariate.

Obtaining effective connectivity networks using uSEM and GIMME

Connectivity patterns among the seven nodes extracted using the above method was determined using uSEM (Kim *et al.* 2007) with models identified using GIMME (Gates & Molenaar 2012; see Supporting Information Appendix S1 for additional details). As described earlier, uSEM considers both contemporaneous and 'lagged' (i.e. ROI status predicting an ROI's status at one TR later) relationships. Including lagged relationships in the model reduces statistical bias (Kim *et al.* 2007; Gates *et al.* 2010) that would otherwise distort the contemporaneous relationships; they do not by themselves represent any interpretable neuronal activity (i.e. the utility of lagged paths are that they enhance the reliability of the contemporaneous model).

Model selection at group and individual levels were conducted using the GIMME program, which has been found to arrive at reliable parameter estimates at much higher rates than most effective connectivity approaches (Gates & Molenaar 2012). First, Lagrange multiplier

equivalents (Sörbom 1989) are used to identify which path (or connection), if freed, would optimally improve model fits across the majority of individuals (set at 75% as informed by the power to detect connections in previous simulations studies). The model is pruned by eliminating the connections which, because of the freeing up of other connections, became non-significant for the majority of individuals.

A primary goal of the current study was to characterize the relationship between variability in cognitive performance and characteristics of effective connectivity among task-related brain regions in nicotine-deprived smokers. Because we sought to explore brain–behavior relationships across a broad range of performance, we divided participants from the composite sample into quartiles based upon their performance on the *n*-back task and compared patterns of effective connectivity across these subgroups. As we were primarily interested in modeling the ability to marshal cognitive resources under very difficult circumstances (e.g. during times of cognitive deficiency), we categorized individuals based upon their performance during the 3-back condition. Quartile subgroups were formed using the signal detection metric d-prime (Snodgrass & Corwin 1988), which takes into account both true positives and false positives to estimate one's ability to distinguish the proper target.

The GIMME program was altered slightly to enable subgroup models at each quartile level. As above, the paths that would optimally improve the majority of individuals' maps were identified in an iterative manner. However, in this step, this search was done within each subgroup using the group map as a foundation. As demonstrated in Gates and Molenaar (2012), only paths that truly exist at the group levels will surface using this procedure. Hence, the group and subgroup maps will only be as complex as the true data are for that subgroup. Finally, individual-level models were estimated in a semi-confirmatory manner, using the subgroup structure as a starting point and Lagrange multiplier equivalents to determine proper path selection (see Supporting Information Appendix S1 for details). The selection process favors parsimonious models; the final models will be only as complex as necessary for that individual.

Examining performance-related differences in connectivity maps

To provide a quantitative test of our primary hypothesis that brain networks are less complex for individuals with higher performance scores, we compared, across quartiles, the number of contemporaneous effects found for individuals' networks using analysis of variance. The number of contemporaneous paths in individual networks provides an index of the overall complexity of each model, with more parsimonious networks suggesting greater efficiency.

RESULTS

Behavioral results

Performance on the *n*-back task is presented in Table 2. Paired samples *t*-tests confirmed that participants had higher accuracy and d-prime scores in the 0-back condition than in the 3-back condition $[t(117) = 12, P < 0.001,$ and $t(117) = 13.9, P < 0.001,$ respectively]. Also, participants were slower in the 3-back condition compared with the 0-back condition, $t(117) = -12.4, P < 0.001$. These results indicate that the 3-back condition was more difficult than the 0-back condition.

fMRI results

Regions exhibiting a main effect of load

Stereotaxic coordinates for the seven brain regions exhibiting a main effect of memory load are presented in Table 3; regions are depicted in Fig. 1. Consistent with expectations, this set included the main brain areas identified as sensitive to increases in working memory load in prior studies using the *n*-back and related tasks. For each ROI, activation during the 3-back condition was

Table 2 Mean (SD) performance on the *n*-back.

Quartile	Condition	Accuracy (%)	d-prime	RT (msec)
<25%	0-back	92.6 (7.9)	3.5 (1.2)	734.2 (221.4)
	3-back	68 (8)	0.78 (1)	838.1 (239)
50%	0-back	94.1 (7.6)	3 (1.6)	611.2 (201.7)
	3-back	80.1 (1.8)	1.5 (0.83)	804.3 (214.6)
75%	0-back	94.3 (8.4)	3.4 (1.7)	666 (200.1)
	3-back	86.4 (1.8)	2 (0.87)	847.6 (188.7)
>75%	0-back	96.1 (4)	3.8 (0.78)	667.3 (134.1)
	3-back	94 (3.4)	3.4 (0.95)	879.8 (177.8)
Full sample	0-back	94.2 (7.3)	3.4 (1.4)	670.4 (197.7)
	3-back	81.4 (10.5)	1.8 (1.3)	840.4 (207.2)

Table 3 Regions exhibiting a significant main effect of memory load (3-back versus 0-back).

| Region | BA | Size (mm³) | MNI Coordinates | | | Average |
			x	y	z	F(1, 116)*
Dorsal ACC/SMA	32/6	5889	−1	22	46	166.4
Left DLPFC	9	2168	−43	25	32	139
Right lateral premotor	6	1992	34	8	54	123.3
Right inferior parietal lobule	40	1113	47	−51	43	122.1
Right DLPFC	9	762	41	29	34	121.9
Left inferior parietal lobule	40	615	−38	−63	46	125.7
Left lateral premotor	6	615	−29	9	58	118.6

*All P values < 0.001.

Note. Coordinates are given for local maxima of activation cluster. ACC = anterior cingulate cortex; BA = Brodmann's area; DLPFC = dorsolateral prefrontal cortex; SMA = supplementary motor area.
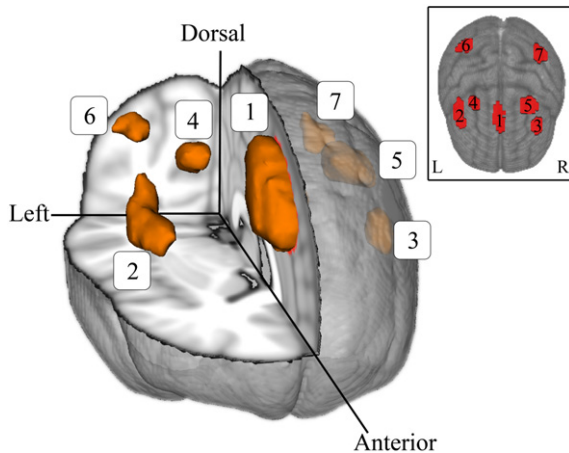

Figure 1 Voxels exhibiting a significant main effect of memory load (3-back versus 0-back). Regions of voxels are numbered as follows: 1 = anterior cingulate cortex/supplementary motor area; 2 = left dorsolateral prefrontal cortex; 3 = right dorsolateral prefrontal cortex; 4 = left lateral premotor cortex; 5 = right lateral premotor cortex; 6 = left inferior parietal lobule; 7 = right inferior parietal lobule

Table 4 Association between *n*-back performance and brain activation (3-back minus 0-back).

Region	Correlation with d-prime (Pearson's r)	P value
Dorsal ACC/SMA	0.16	0.09
Left DLPFC	0.30	0.001*
Right lateral premotor	0.19	0.04
Right inferior parietal lobule	0.22	0.02
Right DLPFC	0.17	0.07
Left inferior parietal lobule	0.20	0.03
Left lateral premotor	0.27	0.003*

*Statistically significant after Bonferroni adjustment (corrected alpha of $P < 0.007$).

Note. ACC = anterior cingulate cortex; BA = Brodmann's area; DLPFC = dorsolateral prefrontal cortex; SMA = supplementary motor area.

significantly greater than activation during the 0-back condition (see Table 3 for statistics).

Association between performance and activation within ROIs

In order to determine the relationship between load-dependent activation within the ROIs and performance on the *n*-back, seven linear regressions were conducted with 3-back d-prime as the dependent factor and brain activation (3-back minus 0-back) as the independent factor. The Bonferroni adjustment was used to control for possible Type I errors associated with multiple comparisons, yielding a corrected alpha of $P < 0.007$ (0.05/7). The results of these regressions are presented in Table 4. Contrary to predictions, task-related activation was positively associated with *n*-back performance for two regions

after applying the Bonferroni correction: left dorsolateral prefrontal cortex (DLPFC), $F(1, 116) = 11$, $P = 0.001$, and left lateral premotor cortex, $F(1, 116) = 9.1$, $P = 0.003$.

Association between performance and effective connectivity among ROIs at the subgroup level

Subgroup-level connectivity maps for each quartile are depicted in Fig. 2. As shown, the top performing group had no additional contemporaneous paths describing their processing beyond those present in the group model for the entire sample. In accordance with our prediction, the average number of contemporaneous paths for individuals differed significantly between the quartiles, $F(3, 114) = 7.29$, $P < 0.001$. A planned contrast revealed a significant linear trend ($P < 0.001$), such that the number of contemporaneous connections decreased from the lowest to the best performing subgroups [mean (standard deviation) number of contemporaneous connections per quartile subgroup: Q1/bottom quartile = 14.0 (1.5); Q2/lower middle quartile = 13.7
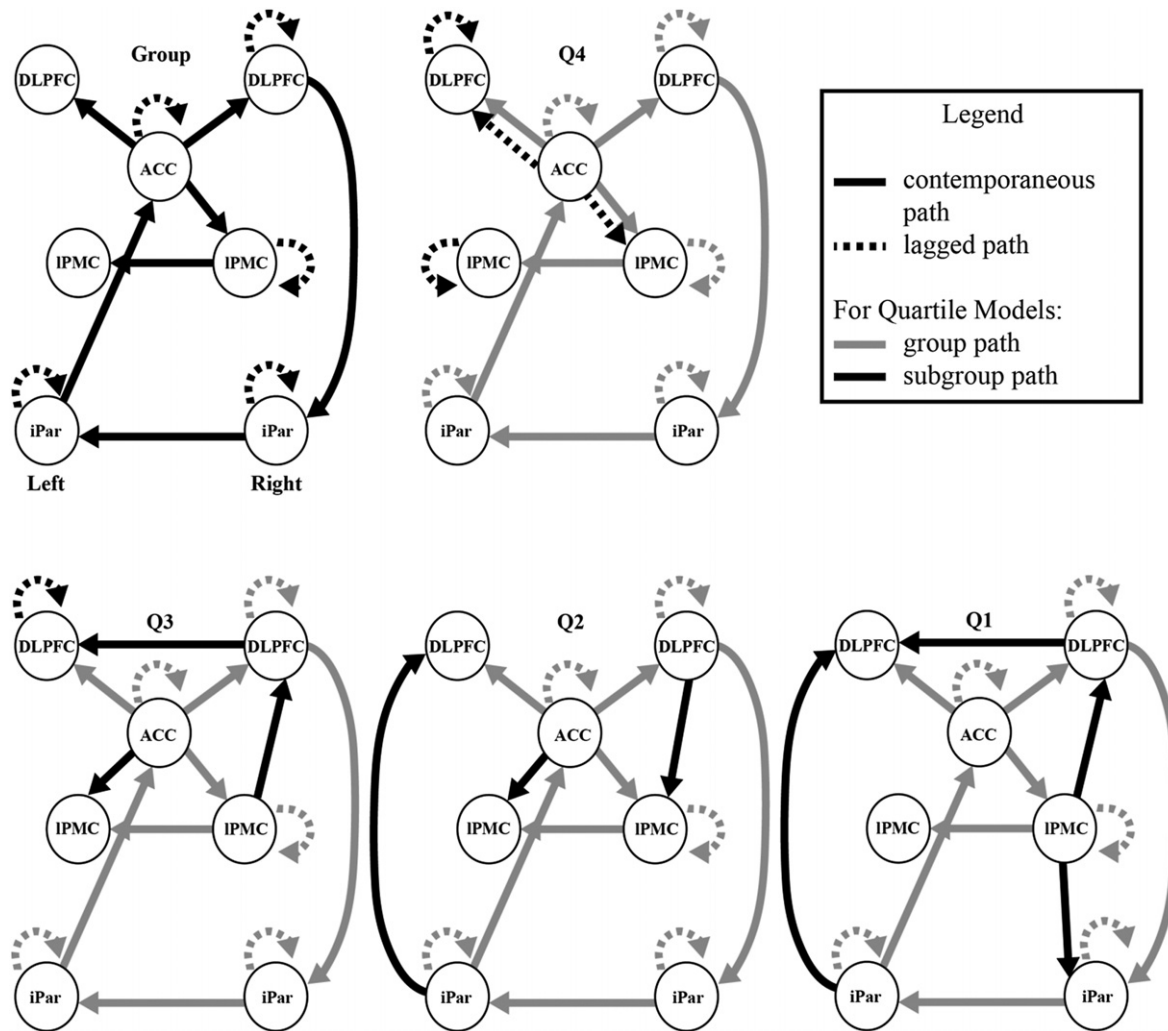
Figure 2 Schematic of group model and subgroup models based on d-prime quartile. Q4 = top performing quartile; Q3 = upper middle quartile; Q2 = lower middle quartile; Q1 = bottom quartile. DLPFC = dorsolateral prefrontal cortex; ACC = anterior cingulate cortex/ supplementary motor area; lPMC = lateral premotor cortex; iPar = inferior parietal lobule

(1.8); Q3/upper middle quartile = 13.0 (1.7); Q4/top quartile = 12.0 (1.8)]. Thus, as hypothesized, network complexity was inversely related to cognitive performance. To explore whether additional relevant factors were related to brain activation and/or network characteristics, we conducted *post hoc* tests examining the association between these variables and smoking-related characteristics (i.e. smoking urge, cigarettes/day and nicotine dependence). Of these, there was a slight but significant negative effect of urge to smoke on the number of connections [$F(1, 116) = 5.36$, $P = 0.02$], but this effect did not survive multiple comparisons correction. No remaining effects were significant ($Ps > 0.4$).

DISCUSSION

The overarching goal of this study was to examine the association between patterns of brain activation and performance during a demanding cognitive task in nicotine-deprived smokers. Our primary objective was to test the hypothesis that deprived smokers who were more successful at the task would exhibit more efficient patterns of brain activation, relative to those who were less successful. Related to this aim, our major finding was that, consistent with our prediction, network complexity (quantified as the number of contemporaneous connections among task-related brain regions) was strongly negatively correlated with performance during the most difficult condition of the *n*-back working memory task. This pattern is reminiscent of the differences between unpracticed and practiced brain networks described by Chein & Schneider (2005). Thus, in line with previous research (e.g. Rypma *et al.* 2006), efficient inter-regional communication (coupled with effective intra-regional processing) appears to be critical for optimal performance during a demanding cognitive task.

Interestingly, while deprived smokers with comparatively better performance during the *n*-back exhibited less complex patterns of effective connectivity than those with poorer performance, the former also tended to exhibit *greater* activation of task-related brain regions than the latter (an effect that survived a correction for multiple comparisons in two regions: the left DLPFC and left lateral premotor cortex). This pattern runs counter to our hypothesis that superior functioning would be linked to reduced activation and underscores the intricacy of load-activation-performance associations. Regarding the latter, Rypma, Berger & D'Esposito (2002) found that individuals with relatively better behavioral performance demonstrated larger increases in DLPFC activation under conditions of escalating memory load—but less activation of the DLPFC overall—than participants with relatively poorer performance. Their results suggest that it is the ability to recruit additional resources as demands intensify, rather than the absolute magnitude of activation, that is important for task success. This capacity is not unbounded; rather, the degree to which task demands drive increases in brain activation is constrained such that increasing load beyond some threshold results in a decrease (e.g. Jaeggi *et al.* 2007) or plateau (e.g. Jaeggi *et al.* 2003) in neural activation.

Previous brain imaging research suggests that nicotine deprivation may impair cognition in part by altering such dynamics; specifically, withdrawal appears to reduce the ability to recruit additional neurocognitive resources under heavy demands (e.g. Jacobsen *et al.* 2007; Kozink *et al.* 2010). For instance, Xu *et al.* (2005) found that activation of the left DLPFC increased concomitant with escalations in memory load during the performance of an *n*-back task when smokers were minimally deprived but did not increase with load after participants abstained from smoking for 14 hours. Results from the current study suggest that there are likely significant individual differences in the magnitude of such state-dependent shifts. More specifically, some deprived smokers appear to have more resources upon which to call to meet the demands of very challenging cognitive tasks (leading to larger increases in the activation of brain areas supporting processes required for the task and better performance) than others.

In addition to highlighting the complicated nature of the links between performance and intraregional changes in activation, results from the present study demonstrate the advantages associated with using advanced statistical methods, such as uSEM and GIMME, to model brain networks. By modeling groups and individuals, we were able to elucidate performance-related individual differences that otherwise were undetected through the use of a standard univariate approach. The use of GIMME, in particular, ensured that the individual-level effective connectivity networks (the basis for testing our primary hypothesis) were reliable. This task alone is difficult (for competing techniques, see Smith *et al.* 2011). By first detecting signal from noise across individuals to arrive at a group model and then identifying individual-level connections in addition to these as needed, GIMME offers the only option to date that has demonstrated ability to arrive at reliable group and individual networks in the presence of heterogeneity (Gates & Molenaar 2012). These unique features of GIMME, when used in combination with a more standard analytic approach, allowed us to determine that better performance by nicotine-deprived smokers was associated with greater within-region activation but more efficient (i.e. less complex) patterns of effective connectivity among brain areas during a difficult cognitive task.

Correlations between *n*-back performance and load-related brain activation were significant but modest. We explored whether other smoking-related variables were related to *n*-back performance but found no significant associations. Most of these factors were also unrelated to network functioning, with the exception of a modest association between urge and network efficiency that failed to survive multiple comparisons correction, as noted above. We also conducted *post hoc* analyses to see if years of education may have impacted cognitive performance or network dynamics. Education was unrelated to 3-back d-prime, load-related BOLD response, and the number of contemporaneous connections ($Ps > 0.1$). Future research investigating additional relevant factors that may be linked to task-related brain activation and/or performance in deprived smokers would be beneficial.

Regarding craving specifically, while the focus of this investigation was on cognitive factors during abstinence and not on craving or withdrawal *per se*, these phenomena are invariably linked. It is possible that we failed to find a relationship between craving and performance in this sample because of insufficient variability in the former, as the sample consisted entirely of nicotine-deprived smokers. Ultimately, more research is needed to identify other factors that contribute to the variability in network functioning and cognitive performance in deprived smokers.

In the absence of the ability to elucidate sources for these individual differences, we can speculate that they may relate to the cognitive strategies used to complete the task (cf. Dunlosky & Kane 2007). For example, poorer performing participants may have used less effective approaches dependent upon a broader array of supporting processes (leading to a greater number of concurrent associations among task-related regions) than better performers. More research is needed to determine the extent to which the additional contemporaneous paths

exhibited by comparatively poorer performers are related to differences in strategy use versus other factors.

Regardless of source, the current findings may have significant clinical implications. As discussed, working memory and attention appear to be critical for the success of attempts to quit smoking (Waters *et al.* 2003; Ilkowska & Engle 2010; Patterson *et al.* 2010). Accordingly, individuals with relatively better working memory and attentional functioning (or show less of a decrement in functioning during acute withdrawal) may be likely to have better outcomes during a quit attempt than those with poorer cognitive functioning. This may be particularly true during the initial hours after quitting when withdrawal-related decrements in cognition are at their peak (Piasecki *et al.* 2003a,b; Hughes 2007; Allen *et al.* 2008). Brain network efficiency may prove to be a useful target for novel approaches to facilitating smoking cessation, such as interventions that integrate recently developed behavioral training strategies for improving attention and working memory (Morrison & Chein 2011).

One limitation of the study is that brain and behavioral responses were not assessed prior to acute nicotine deprivation, so we cannot infer how findings were impacted by withdrawal *per se* (see Supporting Information Appendix S1). While there is abundant evidence establishing withdrawal-related cognitive impairments in smokers, this research could be advanced by clarifying the impact of nicotine deprivation on network functioning (e.g. grouping participants by withdrawal symptoms). Additionally, although important components of nicotine withdrawal (e.g. self-reported craving) were assessed, the study did not include scales specifically designed to measure nicotine withdrawal syndrome; it is possible that additional withdrawal-related effects would have been detected using a more sensitive measure. Nevertheless, the current findings fill an important role in illuminating cognitive functioning in the moment, so to speak, when it is being tested and resources are thinned. Specifically, we showed that different connectivity patterns for effortful cognition exist in a population at risk for relapse. Studies examining the extent to which these differences relate prospectively to smoking outside the laboratory would be informative.

In summary, the current study extends previous research examining effects of nicotine withdrawal on cognition by demonstrating that there is significant variability in cognitive performance among deprived smokers as well as by illuminating neural mechanisms that may underlie these individual differences. Findings indicate that, despite evincing greater load-related increases in brain regions required for the task, deprived smokers with better performance exhibited more 'efficient' patterns of effective connectivity among brain areas than those with worse performance.

Authors Contribution

SJW and TTN were responsible for the study concept and design. KMG and PCMM assisted with data analysis and interpretation of findings. TTN, SJW, and KMG drafted the manuscript. All authors provided critical revision of the manuscript for important intellectual content. All authors critically reviewed content and approved final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1 Supplemental methods, analysis and discussion.