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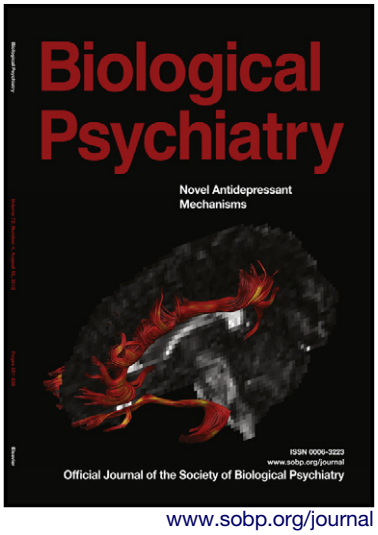

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Neurobiological impact of nicotinic acetylcholine receptor agonists: An ALE meta-analysis of pharmacological neuroimaging studies

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Short Title: Neurobiological impact of nAChR agonists

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ABSTRACT

Background: Nicotinic acetylcholine receptor (nAChR) agonists augment cognition among cigarette smokers and nonsmokers, yet the systems-level neurobiological mechanisms underlying such improvements are not fully understood. Aggregating neuroimaging results regarding nAChR agonists provides a means to identify common functional brain changes that may be related to pro-cognitive drug effects.

Methods: We conducted a meta-analysis of pharmacological neuroimaging studies within the activation likelihood estimation framework. We identified published studies contrasting a nAChR drug condition versus a baseline and coded each contrast by activity change direction (decrease or increase), participant characteristics (smokers or nonsmokers), and drug manipulation employed (pharmacological administration or cigarette smoking).

Results: When considering all studies, nAChR agonist administration was associated with activity *decreases* in multiple regions, including the ventromedial prefrontal cortex (vmPFC), posterior cingulate cortex (PCC), parahippocampus, insula, and the parietal and precentral cortices. Conversely, activity *increases* were observed in lateral frontoparietal cortices, the anterior cingulate cortex (ACC), thalamus, and cuneus. Exploratory analyses indicated that both smokers and nonsmokers showed activity decreases in the vmPFC and PCC, and increases in lateral frontoparietal regions. Among smokers, both pharmacological administration and cigarette smoking were associated with activity decreases in the vmPFC, PCC, and insula, and increases in the lateral PFC, dorsal ACC, thalamus, and cuneus.

Conclusions: These results provide support for the systems-level perspective that nAChR agonists suppress activity in default-mode network regions and enhance activity in executive control network regions in addition to reducing activation of some task-related regions. We speculate these are potential mechanisms by which nAChR agonists enhance cognition.

KEYWORDS: pharmacological functional magnetic resonance imaging (fMRI); activation likelihood estimation (ALE); nicotine; withdrawal; default mode network (DMN); executive control network (ECN).

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INTRODUCTION

Elucidating the neurobiological impact of nicotinic acetylcholine receptor (nAChR) agonists has high translational value (1) given the well-documented attentional and cognitive enhancing properties of nicotine and other nicotine-like drugs. Such drugs augment cognition among cigarette smokers, nonsmokers, and neuropsychiatric patients (2-6) suggesting facilitation beyond nicotine withdrawal reversal. Accordingly, nAChR agonists may provide a productive area of drug development for not only nicotine addiction (7), but also cognitive enhancement when considering healthy individuals (8) and neuropsychiatric conditions such as schizophrenia (9) or attention deficit hyperactivity disorder (10). At the cellular-level, nAChR agonists modulate neuronal activity directly by depolarizing the cell and/or indirectly by altering presynaptic neurotransmission (11-13). To expedite translational applications, enhanced understanding regarding the *systems-level* effects of these drugs on human brain function is of growing interest.

Pharmacological neuroimaging utilizing fMRI or PET is increasingly employed to characterize the impact of an acute drug challenge on human brain function (14-16). Multiple studies have examined nAChR drug-induced brain activity changes following cigarette smoking, nicotine administration (e.g., transdermal patch), or administration of other agonists (e.g., varenicline). Contrasting a nAChR agonist condition with an appropriate baseline provides insight into the functional impact of drug administration. Accordingly, nAChR agonists have been observed to induce heterogeneous changes across the brain, producing decreased activity in some regions, yet increased activity in others. For example, nicotine administration induces activity *decreases* within the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), and angular gyrus, which correlate with behavioral improvements among minimally-deprived

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smokers performing a visuospatial attention task (17). Such activity decreases may manifest as enhanced deactivation of some task-irrelevant regions (17, 18) or reduced activation of some task-related regions (19, 20). Conversely, nicotine administration leads to activity *increases* within the lateral parietal and prefrontal cortices, thalamus, and dorsal anterior cingulate cortex (ACC), which also accompany behavioral improvements among smokers performing a sustained attention task (19, 21). Suggesting that such activity decreases and/or increases are not constrained to task-, participant- or drug-specific manipulations, similar modulations have been observed when considering alternative cognitive domains (18), nonsmokers (22), or varenicline administration (23). As such, aggregating the corpus of pharmacological neuroimaging results regarding nAChR agonists affords the opportunity to identify common functional brain changes that may be related to the pro-cognitive effects of these drugs.

Towards this goal, several recent narrative reviews (24-30), have advocated the perspective that nAChR agonists augment cognition by: 1) decreasing activity in regions subserving task-irrelevant, internally-oriented information processing, 2) concomitantly and reciprocally increasing activity in regions subserving task-related, externally-oriented information processing, and/or 3) decreasing activity in some task-related regions. Moving towards a systems-level conceptualization, such views highlight two large-scale brain networks: the default-mode network (DMN) and the executive control network (ECN). Whereas the DMN, anchored by the mPFC and PCC, is generally associated with internally-oriented thought processes (31), the ECN, composed notably of lateral frontoparietal regions, is generally engaged during attention-demanding tasks (32). Given that evidence suggests an antagonistic relation between DMN and ECN activity (33), intermittent failures to adequately suppress/deactivate DMN regions and activate ECN regions represent putative systems-level mechanisms

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contributing to suboptimal performance (34-36). Accordingly, one mechanism by which nAChR agonists may improve performance is by decreasing activity in some task-irrelevant regions (e.g., DMN structures) while increasing activity in some task-related regions (e.g., ECN structures) thereby promoting a shift from internal to external information processing modes. Although heuristically valuable, narrative reviews are qualitative in nature, often narrowly focused on results from relatively few studies and/or select neuroanatomical structures.

Alternatively, quantitative techniques for meta-analyzing neuroimaging data provide the ability to synthesize and draw inferences from a broad spectrum of studies via a coordinate-based, statistically-driven, whole-brain approach. One such method is activation likelihood estimation (ALE), which identifies locations of significant spatial convergence when considering a corpus of neuroimaging results (37-39). As such, we sought to clarify the neurobiological impact of nAChR agonist administration by meta-analyzing pharmacological neuroimaging results within the ALE framework. We first identified published studies contrasting a nAChR agonist condition versus a baseline condition across a range of neuroimaging paradigms (e.g., cognitive, affective, rest). Subsequently, we coded each identified contrast according to the direction of change induced by drug administration (activity decreases or increases), participant group characteristics (smokers or nonsmokers), and nAChR manipulation method (targeted pharmacological administration or cigarette smoking). In a primary assessment, we examined the overall impact of nAChR agonists to identify regions showing convergent activity modulations. In two exploratory assessments, we further examined the common and distinct effects of drug administration as a function of group (smokers vs. nonsmokers: relevant to cognitive-enhancing applications), and nAChR manipulation method among smokers (pharmacological administration vs. cigarette smoking: relevant to smoking cessation applications).

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METHODS

Study selection. We performed an iterative literature search to compile neuroimaging studies interrogating the functional consequences of nAChR agonist administration. In the first iteration, we searched the *Web of Science* (http://webofknowledge.com) and *PubMed* (http://www.pubmed.gov) databases for peer-reviewed articles published between 2000 and 2013 with the following logical conjunction of terms: ("fMRI" OR "PET" OR "neuroimaging") AND ("nicotine" OR "cigarette" OR "smok*"). In a second iteration, we identified additional studies by consulting the bibliographies of several recent narrative review articles (24-30). While multiple reviews have discussed the impact of nAChR manipulation on human brain function, we note that none have employed a meta-analytic strategy. In a final iteration, we tracked the references of and citations to relevant papers.

We included studies in this meta-analysis that: 1) employed fMRI or PET; 2) reported brain activity changes in stereotaxic coordinates (either Talairach or MNI space); 3) reported a set of coordinates (i.e., foci) from a within-subjects or between-subjects contrast assessing the effects of nAChR agonist administration (i.e., pharmacological administration or cigarette smoking) relative to a baseline condition (i.e., placebo administration or smoking-abstinence condition); and 4) examined brain activity using a cognitive or affective task paradigm or at rest (i.e., in the absence of explicit task demands). Studies examining functional connectivity, brain morphology, or neurochemistry were not included. Given the relatively modest but expanding corpus of literature regarding the impact of nAChR agonists on human brain function, no study exclusions were made on the basis of participant age, neuropsychiatric condition, or statistical threshold considerations.

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Accordingly, we identified 38 studies involving 796 participants and extracted 364 foci from 77 contrasts/experiments for analysis (**Supplemental Tables S1-S2**). Identified studies reported foci obtained by contrasting a nAChR drug manipulation versus a baseline condition and distinguished activity modulation by the baseline > drug (decrease) and drug > baseline (increase) directions. Given that most identified studies involved BOLD-fMRI, the majority of reported foci reflected either a potentiation of task-induced activation (i.e., increase) or deactivation (i.e., a decrease), or a reduction of task-induced activations (i.e., a decrease). In other words, *decreases* may occur either because drug administration was associated with enhanced deactivation or reduced activation of a region. Of the 38 identified studies, 28 studies (179 foci, 39 contrasts) reported activity decreases (Table S1) and 26 studies (185 foci, 38 contrasts) reported increases (Table S2). Given the critical role of nAChRs regarding not only nicotine addiction but also cognitive function among nonsmokers and some neuropsychiatric conditions, we included studies involving both smokers (27 studies: 260 foci, 54 contrasts) and nonsmokers (11 studies: 102 foci, 22 contrasts) with or without a neuropsychiatric diagnosis. Regarding neuropsychiatric conditions, 3 studies (44 foci, 5 contrasts) interrogated the effects of a nAChR agonist in patients diagnosed with schizophrenia. Included studies examined cigarette smokers across a range of smoking states varying from minimal deprivation (0.5-3hrs) to acute abstinence (8-14hrs) to more protracted abstinence (1-3days). Additionally, we coded studies according to nAChR manipulation method as involving either direct pharmacological administration (26 studies: 263 foci, 51 contrasts) or cigarette smoking (12 studies: 101 foci, 26 contrasts). Pharmacological administration methods employed were nicotine delivery strategies (transdermal patch [n=7 studies], nasal spray [n=7], buccal gum [n=5], subcutaneous injection [n=2], and buccal lozenge [n=1]), oral varenicline (n=3; an $\alpha 4\beta 2$ nAChR partial agonist/$\alpha 7$ full

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agonist), or oral DMXB-A (n=1; an α7 nAChR partial agonist). For each study, we also tabulated information on sample characteristics and size, the behavioral paradigm utilized, the neuroimaging modality and analytical strategy employed, and drug-induced effects on behavioral measures (**Supplemental Tables S1-S3**).

ALE images. To interrogate the impact of nAChR agonists on brain function, we performed coordinate-based meta-analyses using the revised version (37) of the ALE algorithm (38, 39) as implemented in *GingerALE v*2.3 (http://brainmap.org/ale/). ALE is a voxel-wise approach for aggregating neuroimaging results to identify locations of significant spatial convergence when considering activity changes across contrasts. This approach treats foci as centers of three-dimensional Gaussian probability distributions thereby accounting for spatial uncertainty. Foci are weighted by study sample size, such that larger samples are associated with "narrower" distributions and smaller samples with "wider" distributions. We first linearly transformed foci reported in MNI to Talairach space (40) and then generated probability/modeled maps of each individual contrast using their associated foci. Subsequently, we calculated a voxel-wise ALE score (i.e., the union of all contrasts' probability maps) quantifying the spatial convergence of activity modulations. To identify clusters of significant convergence, these obtained ALE scores were compared to those from a null distribution (41) derived by repeatedly calculating ALE scores when randomly relocating the same number of input foci. This comparison resulted in non-parametric *p*-value maps, which we then thresholded at a corrected level (described below), converted to *Z*-scores, and exported to *Mango* (http://ric.uthscsa/mango/) for visualization on an anatomical (Talairach) template.

Statistical analyses. We conducted three sets of ALE assessments (one primary and two exploratory) on identified foci (**Figure 1**). In the primary assessment, we first considered the

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OVERALL impact of nAChR agonists on brain function across all identified foci. Specifically, we performed two separate ALE meta-analyses to identify those brain regions associated with significantly convergent activity *decreases* and *increases*. We thresholded the resulting ALE images at a cluster-level of $p_{corrected}<0.05$ (voxel-wise: $p_{FDR\text{-}corrected}<0.01$; minimum cluster: 488mm³[decreases], 344mm³[increases]).

In the first exploratory assessment, we again performed separate meta-analyses focusing on activity *decreases* and *increases*, but here, we fractionated foci by *GROUP* to examine common and distinct effects among smokers and nonsmokers. We first derived ALE images separately for smokers and nonsmokers employing a more lenient threshold than described above ($p_{FDR\text{-}corrected}<0.05$; minimum cluster: 250mm³). To identify common group effects, we next performed a conjunction analysis with the two groups' thresholded ALE images (smoker ∩ nonsmoker) and created conjunction maps indentifying clusters (minimum extent: 45mm³) surviving threshold in both. To identify distinct group effects, exploratory contrast analyses were also simultaneously performed along with this conjunction analysis. We identified clusters showing significant group differences (i.e., smoker > nonsmoker, smoker < nonsmoker) using a $p_{FDR\text{-}corrected}<0.05$ threshold (minimum cluster: 250mm³).

In the second exploratory assessment, we further parsed foci from smokers by nAChR *MANIPULATION* method to isolate the common and distinct effects of pharmacological administration and cigarette smoking. Employing the same thresholds described for the former assessment, we derived separate ALE images for both manipulation methods and performed a conjunction analysis to identify common effects (pharmaco ∩ smoking) and contrast analyses to identify distinct effects (pharmaco > smoking, pharmaco < smoking).

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RESULTS

OVERALL impact of nAChR agonists. To elucidate brain regions modulated by nAChR agonist administration, we first conducted two meta-analyses identifying convergent activity *decreases* and *increases* (**Figure 2**, **Table 1**). When considering all foci, nAChR agonists were associated with activity *decreases* in the ventromedial PFC (vmPFC), subgenual ACC, PCC, right parahippocampus, bilateral insulae, right superior parietal cortex, and right precentral cortex (Figure2, blue). Further characterization of these activity decreases, revealed that modulations in the vmPFC, PCC, and parahippocampus reflected enhanced deactivations whereas modulations in the subgenual ACC, bilateral insulae, and the parietal, and precentral cortices reflected reduced activations (**Supplemental Figure S1**). Conversely, nAChR agonists were associated with activity *increases* in the dorsomedial PFC (dmPFC), dorsal ACC, thalamus, cuneus, lingual gyrus, and lateral prefrontal and parietal cortices (Figure2, red). Additionally, we conducted multiple ancillary analyses to more precisely characterize the behavioral domain and analytical context in which these activity decreases and increases were observed (**Supplemental Figures S2-S6**, **Tables S4-S6**).

Common and distinct GROUP effects. To explore common and distinct drug-induced effects among smokers and nonsmokers, we next conducted separate meta-analyses (*decreases* and *increases*) fractionating foci by *GROUP*. Subsequently, we performed conjunction analyses to identify common effects and, simultaneously, contrast analyses to identify distinct effects (**Figure 3**, **Supplemental Table S7, Figure S7**).

With respect to *common* GROUP effects involving activity *decreases*, the conjunction analysis revealed overlap notably in the vmPFC, PCC, and right inferior parietal cortex (Figure3A, green). When considering *common* GROUP effects involving activity *increases*, the

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conjunction analysis revealed overlap notably in the cingulate, left dorsolateral PFC (dlPFC), and left inferior parietal cortex (Figure3B, green).

With respect to *distinct* GROUP effects involving activity *decreases*, directly contrasting the two groups' ALE results revealed that nonsmokers (smokers < nonsmokers) were more likely to show decreases in the right inferior parietal cortex (Figure3A, purple). No clusters were identified in the reverse contrast (smokers > nonsmokers). When considering *distinct* GROUP effects involving activity *increases*, smokers (smokers > nonsmokers) were more likely to show increases in the right dlPFC (Figure3B, orange), whereas nonsmokers (smokers < nonsmokers) were more likely to show increases notably in the bilateral parietal cortices, right middle frontal gyrus, and ACC (Figure3B, purple).

Common and distinct MANIPULATION effects. To explore the common and distinct effects of pharmacological administration and cigarette smoking, we lastly compared and contrasted the ALE results (*decreases* and *increases*) produced when parsing foci from cigarette smokers by *MANIPULATION* method (**Figure 4**, **Supplemental Table S8**, **Figure S8**). With respect to *common* MANIPULATION effects involving activity *decreases*, the conjunction analysis revealed overlap notably in the vmPFC, subgenual ACC, PCC, and left mid-insula (Figure4A, green). When considering *common* MANIPULATION effects involving *increases*, the conjunction analysis revealed overlap notably in the dorsal ACC, thalamus, cuneus, and right dlPFC (Figure4B, green).

With respect to *distinct* MANIPULATION effects involving activity *decreases*, directly contrasting the two ALE results revealed that cigarette smoking (pharmaco < smoking), was more likely associated with activity decreases in the right anterior insula (Figure4A, purple), whereas pharmacological administration (pharmaco > smoking) was more likely associated with

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decreases in the lingual gyrus (Figure4A, orange). When considering *distinct* MANIPULATION effects involving activity *increases*, pharmacological administration (pharmaco > smoking) was more likely associated with increases in the dorsal ACC and neighboring medial frontal gyrus (Figure4B, orange). No clusters were identified in the reverse contrast (pharmaco < smoking).

DISCUSSION

We aggregated pharmacological neuroimaging results regarding nAChR agonists to clarify the impact of these drugs on human brain function. Our meta-analytic results revealed convergent activity *decreases* in multiple regions including the vmPFC, PCC, and right parahippocampus (i.e., canonical DMN regions) as well as in the right superior parietal cortex, right precentral gyrus, and bilateral insulae (i.e., task-related regions). In contrast, convergent activity *increases* were observed in lateral frontoparietal cortices (i.e., core ECN regions) as well as in the dorsal ACC, thalamus, and cuneus. These results provide quantitative meta-analytic support for the systems-level perspective that nAChR agonists reduce activity in some DMN regions and enhance activity in some task-related regions including those comprising the ECN in addition to reducing activation in some task-related regions. Suggesting that these modulations are not constrained to the amelioration of smoking deprivation-induced effects, we observed that both smokers and nonsmokers showed activity decreases in the vmPFC and PCC as well as increases in lateral frontoparietal cortices. Suggesting a desirable characteristic of future smoking cessation interventions, we observed among smokers that both pharmacological administration and cigarette smoking were associated with activity decreases in the vmPFC, PCC, and insula as well as increases in the lateral PFC, dorsal ACC, thalamus, and cuneus.

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OVERALL impact of nAChR agonists. Cognitively demanding tasks deactivate DMN regions and activate regions within the ECN (35, 42, 43). A failure to adequately deactivate DMN regions contributes to sub-optimal task performance (34, 44, 45) possibly due to persistent engagement of internally-oriented information processing. As such, enhanced DMN suppression, coupled with increased activation of some task-related regions including those within the ECN, represents a plausible systems-level mechanism by which nAChR agonists augment cognition (17, 24-29). Our meta-analytic results regarding the overall impact of drug administration are consistent with this deactivation-activation pattern. One interpretation is that such neuromodulation mediates a shift from internally-oriented information processing towards a state more conducive to processing external stimuli. This systems-level view parallels acetylcholine's role in toggling circuit dynamics at the cellular-level between cortico-cortical feedback (low acetylcholine) and thalamo-cortical feed-forward states (high acetylcholine) (18, 24, 46, 47). Providing a link between these systems-level effects and alterations in cognition, activity decreases within the mPFC and PCC as well as increases within lateral prefrontal regions have been associated with improved task performance (17, 23).

While activity decreases following nAChR agonist administration reflect enhanced deactivation of some regions (17, 18, 21, 23), they reflect less task-induced activation of others (18-20, 23, 48). The convergent activity decreases we identified in the right superior parietal cortex, right precentral gyrus, and bilateral insulae are consistent with the latter effect (Supplemental FigureS4). One interpretation of reduced task-induced activation that also accompanies equal or augmented performance following nAChR agonist administration is enhanced cortical processing efficiency (24). For example, less task-induced activation in superior parietal and precentral regions following nicotine administration has been suggested to

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reflect improved efficiency in shifting attention away from distracting stimuli during visuospatial reorienting (20, 48), working memory (49), and Stroop task performance (50). Another potential interpretation of decreased activity relates to the amelioration of distracting physiological or affective states and, in turn, a reduced demand for attentional control resources (24). This perspective may be particularly relevant when considering activity reductions in the insula given the region's roles in monitoring homeostatically-relevant bodily sensations (51, 52) as well as initiating, maintaining, and adjusting attentional resources (53, 54).

Common and distinct GROUP effects. While we observed distinct effects when separately considering studies involving smokers or nonsmokers, the conjunction of the two groups' ALE results revealed overlapping decreases notably in the vmPFC and PCC, as well as overlapping increases in lateral frontoparietal cortices. These outcomes suggest that the ability of nAChR agonists to reduce activity in DMN regions and enhance activity in ECN regions is not limited to individuals with an extended smoking history, but rather may be a more general neuropharmacological effect. However, such effects are likely more evident among individuals experiencing state- (e.g., nicotine withdrawal) or trait-related (e.g., neuropsychiatric conditions) cognitive deficits (6). Given that multiple neuropsychiatric conditions are associated with altered DMN and ECN dynamics in general and reduced DMN suppression in particular (27, 35, 43, 55), these meta-analytic results provide neurobiological support for the potential therapeutic utility of nAChR agonists.

Regarding distinct effects, the dlPFC was more likely to show drug-induced activity increases in studies involving cigarette smokers. While we consider the results of our exploratory assessments preliminary, this observation is consistent with neuroadaptive changes associated with an extended smoking history (e.g., nAChR upregulation: 56). Critically, dlPFC

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hypoactivation among smokers likely contributes to working memory deficits, which are predictive of smoking relapse (23, 57-59). The current results provide support for the utility of considering dlPFC activity as a potential interventional target for smoking cessation (23, 60, 61). Conversely, our results indicated that the bilateral parietal cortices, right middle frontal gyrus, and ACC were more likely to show drug-induced activity increases in studies involving nonsmokers. Additionally, nonsmokers were more likely to show activity decreases in a right inferior parietal region immediately adjacent to a cluster common to both groups. We consider these outcomes with caution given the file drawer problem associated with a potential publication bias toward significant results (62, 63), particularly when considering the limited number of studies involving nonsmokers.

Common and distinct MANIPULATION effects. While we observed distinct effects when separately considering studies manipulating smokers' nAChRs via direct pharmacological administration or cigarette smoking, the conjunction of these manipulation-specific ALE results revealed overlapping decreases in the vmPFC, PCC, and left mid-insula. In contrast to the current drug-induced activity *decreases*, smoking cue-induced activity *increases* have been consistently observed in these same regions and/or to correlate with subjective tobacco craving (64-68). As such, we speculate that decreased activity in DMN regions and the insula, in addition to enhancing externally-oriented information processing, may contribute to reduced smoking motivation. The insula and its functional interactions with other brain regions appear critically linked with motivational processes perpetuating drug use (69-73). For example, abstinence-induced alterations in the functional connectivity between the insula, DMN, and ECN may contribute to tobacco craving (74) and nAChR agonists reduce connectivity between the insula and DMN regions among overnight-abstinent smokers (75). As such, a desirable characteristic of

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smoking cessation interventions may be to reduce activity in (and/or the functional connectivity between) task-irrelevant/DMN regions and the insula, while concurrently, enhancing activity in task-related/ECN regions (27, 28). In line with this suggestion, we note that another recent meta-analysis interrogating the neurobiological targets of pharmacological and cognitive-based treatments for addiction to various drugs (including nicotine) identified similar (e.g., vmPFC and PCC/precuneus) and additional brain regions (e.g., the ventral striatum) (76).

Regarding distinct effects, the right anterior insula was more likely to show activity decreases in studies employing a smoking manipulation. Bearing in mind the exploratory nature of these outcomes, it is notable that the anterior insula has been conceptualized as a critical neural substrate for subjective emotional experiences and awareness (51, 77) with an emphasis on the right anterior insula regarding arousing or aversive states (52, 78). Higher activity in the anterior insula consistently correlates with subjective tobacco craving (79) as do structural alterations in the right anterior insula (80). On the other hand, the lingual gyrus was more likely to show activity decreases in studies involving a direct pharmacological manipulation. This region shows consistent activity increases to smoking-related stimuli and a decrease in such activity may be indicative of lower incentive salience for drug cues (65). Lastly, the dorsal ACC and medial frontal gyrus were more likely to show activity increases in pharmacological administration studies. Increased activity in these regions may promote improved performance monitoring and inhibitory control, psychological constructs often impaired in addiction (81, 82)

Limitations and conclusions. Our findings should be considered in light of several remaining issues. First, outcomes from our exploratory analyses assessing group- and manipulation-specific effects should be considered preliminary given the modest number of foci when parsing studies by such characteristics. This limitation also precluded examination of drug

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effects as a function of smoking state (e.g., minimally-deprived vs. abstinent smokers). Second, as all meta-analyses are based on available data, their results may be influenced by biases in the literature. For example, the range of cognitive paradigms interrogated with respect to nAChR agonists predominately has been restricted to visuospatial attention, sustained attention, selective attention, and working memory. Although limited, given the range of neuroimaging paradigms included, we note that our results reflect drug-induced effects on brain activity that are task independent. As additional neuroimaging data accumulate it will become possible to more precisely characterize task-specific effects (although see: Supplemental Figures S2-S3). Third, meta-analytic results are limited by the design of the included studies. With respect to pharmacological fMRI studies, potential nonspecific effects on cerebral blood flow and/or alterations in neurovascular coupling, as opposed to modulations of neuronal activity, represent alternative explanations (although see: 83). Mitigating concern for such issues, nAChR agonists do not alter the BOLD signal or cerebral blood flow during simple visuomotor stimulation (17). Our observation of convergent decreases in some regions and yet increases in others, also argues against nonspecific effects.

In sum, nAChR agonist administration involves multiple region-specific effects (i.e., increases and decreases [including enhanced deactivations and reduced task-induced activations]). Our results bolster the view that nAChR agonists decrease activity in DMN regions and increase activity in task-related regions (while also decreasing task-induced activation in some regions). These meta-analytic outcomes point toward a common neurobiological mechanism at the systems-level by which nAChR agonists may enhance cognition and/or reduce tobacco craving. A systems-level understanding of the neuropharmacological properties of

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nicotinic agents may expedite development of improved interventions for not only smoking cessation but also other conditions characterized by compromised attentional processes.

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FINANCIAL DISCLOSURE

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

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TABLES

Table 1. Overall impact of nAChR agonists: Coordinates of identified clusters.

Cluster	Region		Volume	x	y	z
Decreases						
1)	Anterior cingulate (BA32)(vmPFC)	B	1272	-8	46	0
2)	Anterior cingulate (BA24)(subgenual)	B	840	0	30	-2
3)	Posterior cingulate (BA23)	B	1072	-2	-56	14
4)	Parahippocampal gyrus	R	1048	28	-14	-14
5)	Insula(anterior)/claustrum	R	760	30	14	4
6)	Insula (BA13)	L	1008	-36	2	12
7)	Superior parietal lobule (BA7)	R	992	30	-52	40
8)	Precentral gyrus (BA3)	R	568	34	-28	50
	Insula (BA13)	R	496	34	-4	20
Increases						
a)	Medial frontal gyrus (BA9)(dmPFC)	B	1016	3	42	17
b)	Anterior cingulate (BA32) (dorsal)	B	4032	0	22	34
c)	Thalamus	B	1792	-8	-16	10
d)	Cuneus (BA23)	L	400	-6	-74	8
e)	Lingual gyrus (BA18)	L	392	-6	-88	-14
f)	Inferior frontal gyrus (BA47)	R	592	30	18	-18
g)	Insula/claustrum	L	672	-36	-4	4
h)	Middle frontal gyrus (BA9)(dlPFC)	R	656	48	20	28
i)	Supramarginal gyrus (BA40)	R	400	54	-48	26
j)	Middle frontal gyrus (BA8)(dlPFC)	L	1536	-24	26	44
k)	Precentral gyrus (BA6)	L	944	-52	4	36
l)	Inferior parietal lobule (BA40)	L	448	-52	-46	40
m)	Superior parietal lobule	L	1080	-28	-56	44
n)	Precentral gyrus (BA6)	R	528	50	2	42
o)	Inferior parietal lobule (BA40)	R	384	56	-44	38
	Superior temporal gyrus (BA38)	R	464	36	6	-24
	Cerebellum (posterior lobe)	R	368	20	-80	-30
	Caudate (body)	R	368	10	-4	14
	Middle frontal gyrus (BA46)(dlPFC)	R	344	40	32	18

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Note. Numbering (Decreases, top) and lettering (Increases, bottom) correspond to brain regions shown in **Figure 2**. Coordinates (x, y, z) of the clusters' peak voxels are report in Talairach space. R: right; L: left, B: bilateral; volume: mm^3.

FIGURE LEGENDS

Figure 1. Schematic illustration of meta-analytic assessments. Foci from included contrasts were coded according to direction of change (decreases: blue; increases: red), participant *GROUP* (nonsmoker or smoker) and nAChR *MANIPULATION* method (pharmacological administration or cigarette smoking). *One study (2 foci, 1 contrast) was excluded from the *GROUP* assessment as the reported drug effect was collapsed across smokers and nonsmokers.

Figure 2. Overall impact of nAChR agonist administration. Across all studies, nAChR agonists were associated with decreased activity (blue; baseline > drug) notably in the vmPFC, subgenual ACC, PCC, right parahippocampus, and bilateral insulae. In addition, nAChR agonists were associated with increased activity (red; drug > baseline) notably in the dmPFC, dorsal ACC, thalamus, cuneus, lingual gyrus, and lateral prefrontal and parietal regions. Functionally defined and publically available templates (84) of the DMN (purple transparency) as well as the left and right ECN (yellow transparency) are overlaid for visualization of overlap between convergent activity modulations and these large-scale networks. Numbering (decreases) and lettering (increases) correspond to coordinates listed in **Table 1**. See **Supplemental Figures S1-S5** and **Tables S4-S5** for ancillary analyses further characterizing the nature of and context in which these activity modulations were observed. See **Supplemental Figure S6** and **Table S6** for statistical comparison between these two ALE images.

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Figure 3. Group effects: Common and distinct drug-effects among smokers and nonsmokers. **A**) Decreases: Among both groups, nAChR agonists were associated with activity decreases overlapping in the vmPFC, PCC, and right inferior parietal cortex (green). Nonsmokers showed greater decreases in the right inferior parietal cortex (purple). **B**) Increases: Among both groups, nAChR agonists were associated with activity increases overlapping in the cingulate gyrus, left dlPFC, and left inferior parietal cortex (green). Smokers showed greater increases in the right dlPFC (orange), while nonsmokers showed greater increases in bilateral parietal, right prefrontal, and cingulate regions (purple). See **Supplemental Table S7** for the complete list of identified clusters and corresponding coordinates. See **Supplemental Figure S7** for the separate ALE images from the two groups.

Figure 4. Manipulation effects (smokers only): Common and distinct impact of pharmacological administration and cigarette smoking. **A**) Decreases: Pharmacological administration and smoking were associated with activity decreases overlapping in the vmPFC, subgenual ACC, PCC, and left mid-insula (green). Cigarette smoking was associated with greater decreases in the right anterior insula (purple), whereas pharmacological administration was associated with greater decreases in the lingual gyrus (orange). **B**) Increases: Pharmacological administration and cigarette smoking were associated with activity increases overlapping in the dorsal ACC, thalamus, cuneus and dlPFC (green). Pharmacological administration was associated with greater increases in the ACC (orange). See **Supplemental Table S8** for the complete list of identified clusters and corresponding coordinates. See **Supplemental Figure S8** for the separate ALE images from the two manipulation methods.

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FIG 1

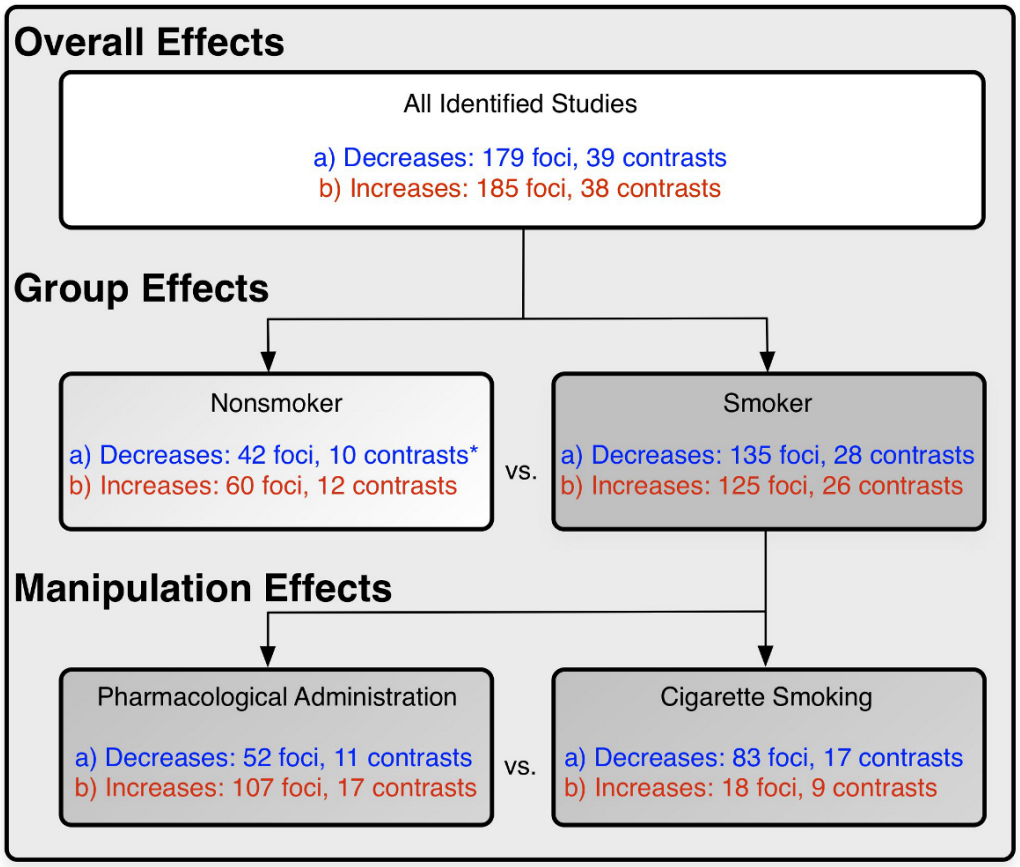

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FIG 2

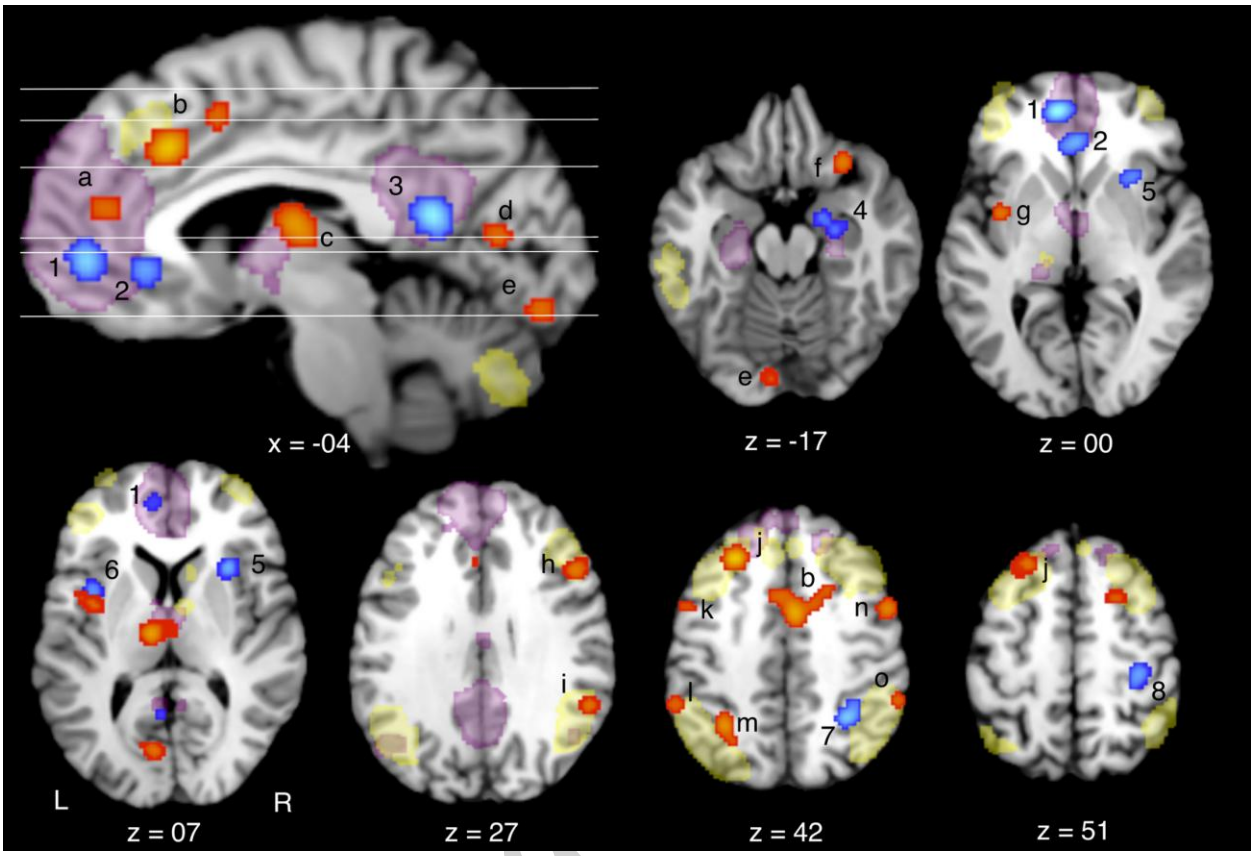

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FIG 3

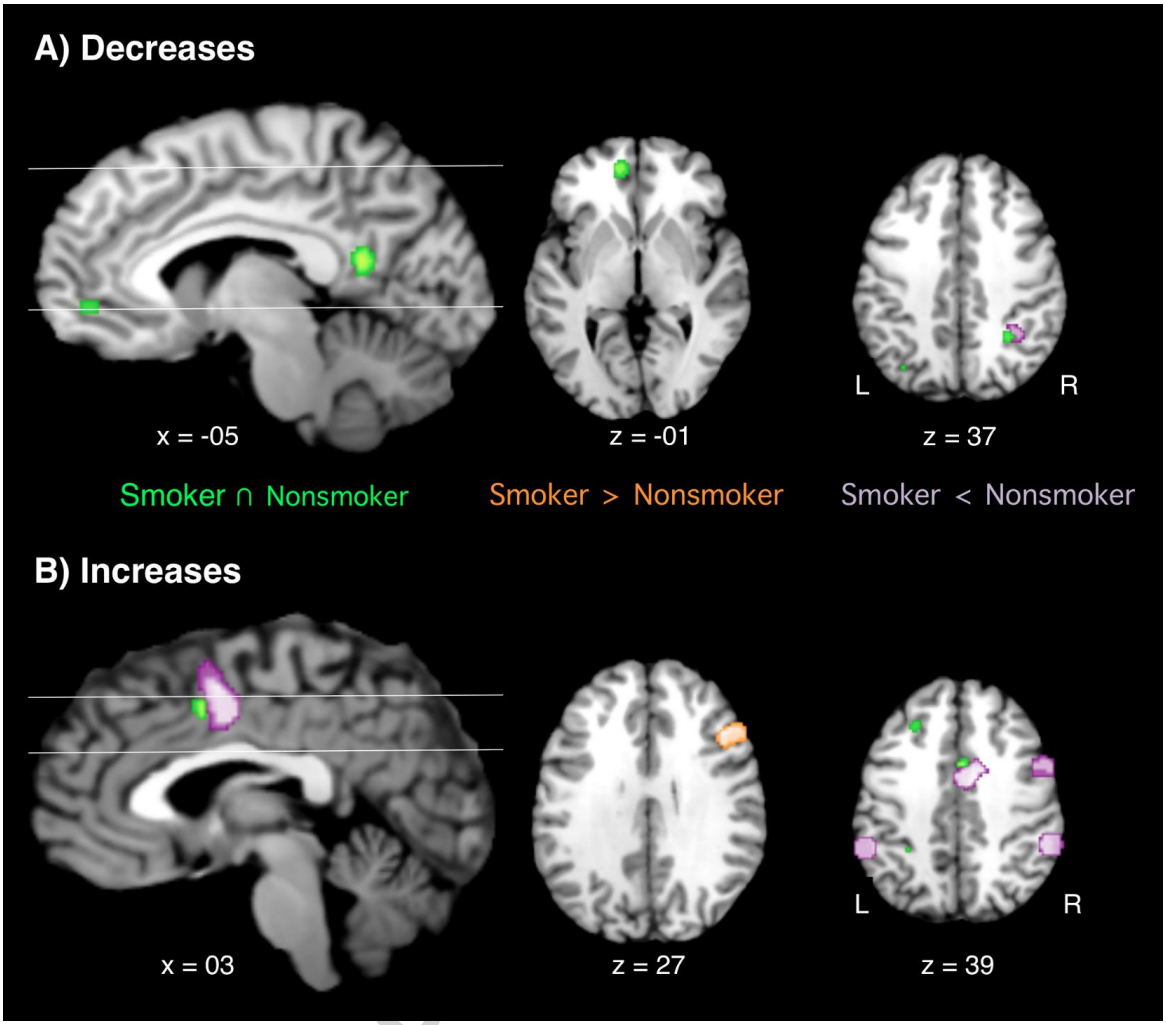
A) Decreases
x = -05
z = -01
L
R
z = 37
Smoker ∩ Nonsmoker
Smoker > Nonsmoker
Smoker < Nonsmoker
B) Increases
x = 03
z = 27
L
R
z = 39

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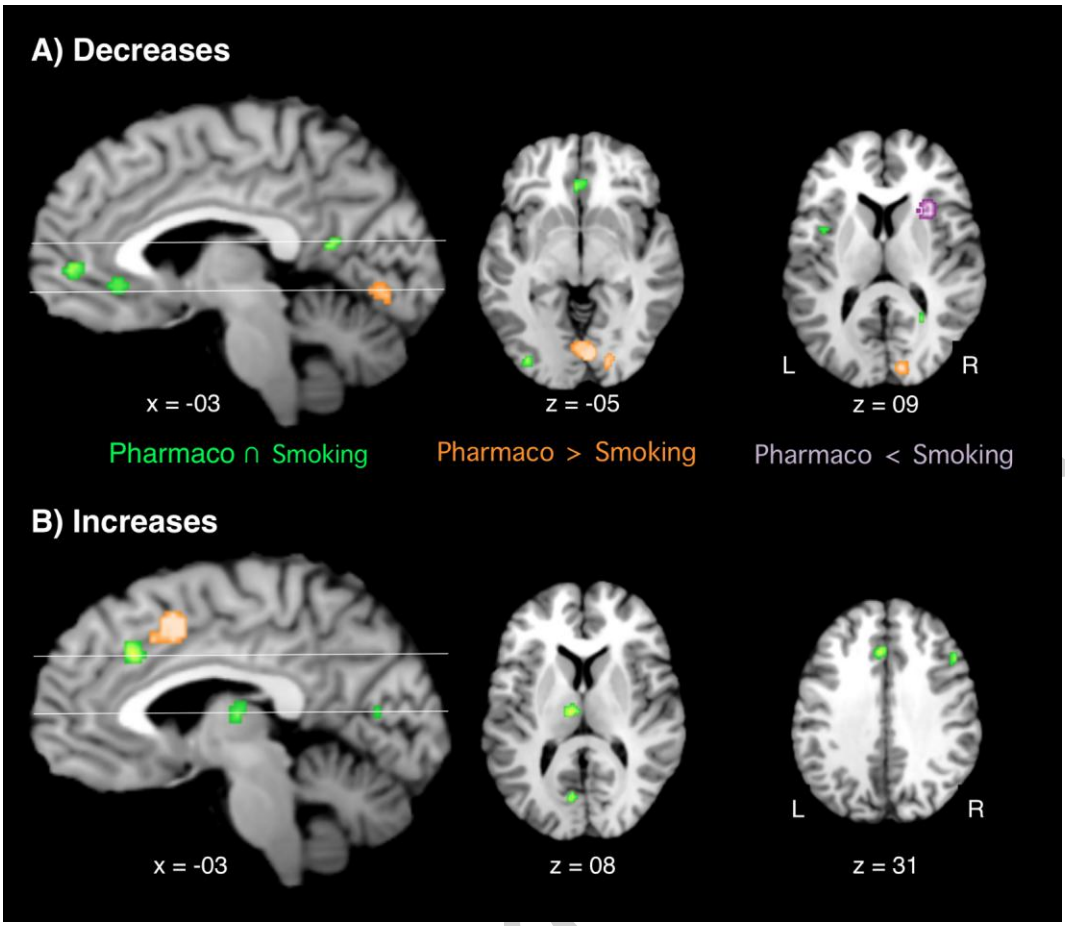
FIG 4



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