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Neurobiological Impact of Nicotinic Acetylcholine Receptor Agonists: An Activation Likelihood Estimation Meta-Analysis of Pharmacologic Neuroimaging Studies

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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 procognitive drug effects.

METHODS: We conducted a meta-analysis of pharmacologic 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 (pharmacologic 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, 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 pharmacologic administration and cigarette smoking were associated with activity decreases in the vmPFC, PCC, and insula and increases in the lateral PFC, dorsal anterior cingulate cortex, 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: Activation likelihood estimation (ALE), Default mode network (DMN), Executive control network (ECN), Nicotine, Pharmacologic functional magnetic resonance imaging (fMRI), Withdrawal

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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.

Pharmacologic neuroimaging utilizing functional magnetic resonance imaging (fMRI) or positron emission tomography (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

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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 that correlate with behavioral improvements among minimally deprived 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) that 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 pharmacologic neuroimaging results regarding nAChR agonists affords the opportunity to identify common functional brain changes that may be related to the procognitive effects of these drugs.

Toward 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 toward 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 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 pharmacologic 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 pharmacologic 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 (pharmacologic administration vs. cigarette smoking: relevant to smoking cessation applications).

METHODS AND MATERIALS

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 (Thomson Reuters, New York, New York; http://webofknowledge.com) and PubMed (National Center for Biotechnology Information, Bethesda, Maryland; 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 Montreal Neurological Institute 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., pharmacologic 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.

Accordingly, we identified 38 studies involving 796 participants and extracted 364 foci from 77 contrasts/experiments for analysis (Tables S1 and S2 in Supplement 1). Identified studies reported foci obtained by contrasting a nAChR drug manipulation versus a baseline condition and distinguished