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Nicotinic modulation of salience network connectivity and centrality in schizophrenia

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ABSTRACT

Although functional abnormalities of the salience network are associated with schizophrenia, the acute effects of nicotine on its function and network dynamics during the resting state in patients are poorly understood. In this study, the effects of a 7 mg nicotine patch (vs. placebo) on salience network connectivity were examined in 17 patients with schizophrenia and 19 healthy subjects. We hypothesized abnormal connectivity between the salience network and other major networks (e.g. executive network) in patients under placebo administration and amelioration of this difference after nicotine. We also examined effects of nicotine on betweenness centrality (a measure of the influence of a region on information transfer throughout the brain) and local efficiency (a measure of local information transfer) of the network. A hybrid independent component analysis (ICA)/seed-based connectivity approach was implemented in which the salience network was extracted by ICA and cortical network peaks (anterior cingulate cortex (ACC), left and right insula) were used as seeds for whole-brain seed-to-voxel connectivity analysis. Significant drug X diagnosis interactions were observed between the ACC seed and superior parietal lobule and ventrolateral prefrontal cortex. A significant interaction effect was also observed between the left insula seed and middle cingulate cortex. During placebo conditions, abnormal connectivity predicted negative symptom severity and lower global functioning in patients. A significant drug X diagnosis interaction was also observed for betweenness centrality of the ACC. These results suggest that nicotine may target abnormalities in functional connectivity between salience and executive network areas in schizophrenia as well as affect the ability of the salience network to act as an integrator of global signaling in the disorder.

1. Introduction

The brain is constantly bombarded by information from the external environment and internal sources. In order to produce an appropriate response and form a coherent experience of the world (i.e. our concept of "reality") the brain must be able to constantly filter, integrate, and evaluate this information. This moment-to-moment evaluation is a major function of the salience network, a functionally (Menon, 2015) and structurally (Uddin et al., 2011; van den Heuvel et al., 2009) connected set of brain areas that includes the anterior insular and anterior cingulate cortices (ACC). The salience network is able to accomplish this task through its functional connectivity to diverse brain areas. These include regions involved in executive function (e.g. prefrontal cortex and superior parietal cortex) as well as to areas that comprise the "default mode network" (DMN) (e.g. posterior cingulate cortex, inferior parietal cortices and preceneus) (Menon and Uddin, 2010). Indeed, due to its patterns of intrinsic connectivity, the salience network may be involved in switching between executive and default-mode dominant states based on task demands (Menon, 2011; Menon and Uddin, 2010; Palaniyappan and Liddle, 2012).

Given that the salience network may play a key role in how we perceive the world and consequently shape our reality, it perhaps comes as no surprise that dysfunction of the network is increasingly believed to play a cardinal role in psychosis and

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schizophrenia. Indeed, salience network dysfunction may also play a critical role in explaining the negative and cognitive symptoms of the illness. Cognitive symptoms may involve the inability to appropriately switch between networks. Negative symptoms suggest that patients are unable to act appropriately based on circumstances. In support of this view, previous work has demonstrated that the salience network is functionally, structurally, and neurochemically abnormal in schizophrenia (reviewed by Palaniyappan and Liddle (2012); Palaniyappan et al. (2012); Smucny and Tregellas (2013); Wylie and Tregellas (2010)). Resting-state functional magnetic resonance imaging (fMRI) studies have reported abnormal salience network connectivity in schizophrenia, including within the network (Kraguljac et al., 2016; Pu et al., 2012) and between the network and other networks (Manoliu et al., 2014; Moran et al., 2013b; Palaniyappan et al., 2013; Pelletier-Baldelli et al., 2015). Finally, salience network dysfunction has been linked to all three domains of symptoms in schizophrenia (Kuhn and Gallinat, 2012; Lahti et al., 2006; Manoliu et al., 2013; Palaniyappan et al., 2013).

Given that the salience network may play a key role in understanding the symptoms of schizophrenia, it follows that pharmacologically targeting the network may have clinical utility. One highly studied class of drugs in schizophrenia is nicotinic agonists. Interest in these drugs is due to high rates of smoking (~70%) in the illness (Winterer, 2010) leading researchers to hypothesize that nicotine may be a form of "self medication" (Winterer, 2010). In schizophrenia, acute nicotine has been shown to improve cognition as well as target abnormal brain function (Barr et al., 2008; Harris et al., 2004; Smucny et al., 2016a, 2016b, 2015; Tregellas et al., 2011; Wylie et al., 2016). Conversely, the nicotinic antagonist mecamylamine worsens cognitive performance in patients (Roh et al., 2014). Aberrant salience network function is associated with smoking status in schizophrenia (Moran et al., 2013a), targeted by nicotine in healthy deprived cigarette smokers (Hong et al., 2009; Sutherland et al., 2013), and may be a critical system underlying nicotine addition (reviewed by Sutherland et al., 2012). Finally, all three nodes of the salience network highly express nicotinic receptors (Breese et al., 1997; Paterson and Nordberg, 2000; Picard et al., 2013), suggesting the network may be effectively targeted by nicotine and other nicotinic agents.

To examine the effects of pharmacologic treatment on brain network connectivity, researchers most frequently adopt seed-based (connectivity between a seed and other regions) or multivariate (e.g. independent components analysis (ICA)) approaches. To take these analyses a step further, topological analysis or "graph theory" can be used to ascertain the organizational principles that underlie functional intrinsic networks. One interesting topological metric is *betweenness centrality*, a term that describes how frequently a brain region is used to enable one area to communicate with another. A node (e.g. brain region) with high betweenness centrality is frequently used to traverse from any region in a network of brain regions to any other region (Fig. 1, top). Related to this point, the relatively high betweenness centrality of the salience network may drive its ability to integrate information and process salience (van den Heuvel and Sporns, 2013). Furthermore, previous studies suggest that betweenness centrality of the ACC may be disrupted in schizophrenia and in at-risk populations (Lord et al., 2011, 2012; van den Heuvel et al., 2010).

In contrast to betweenness centrality, analysis of *local efficiency* examines communication solely between a node (e.g. brain region) and its "neighbors" (other regions directly connected to that region) and is therefore a measure of local (rather than global) information integration. Neighbors surrounding a node with high local efficiency are able to communicate between themselves without having to traverse between many other nodes (Fig. 1, bottom). Disrupted local efficiency has been observed in schizophrenia patients in a number of areas, including the ACC (Smucny and Tregellas, 2013; Yan et al., 2015).

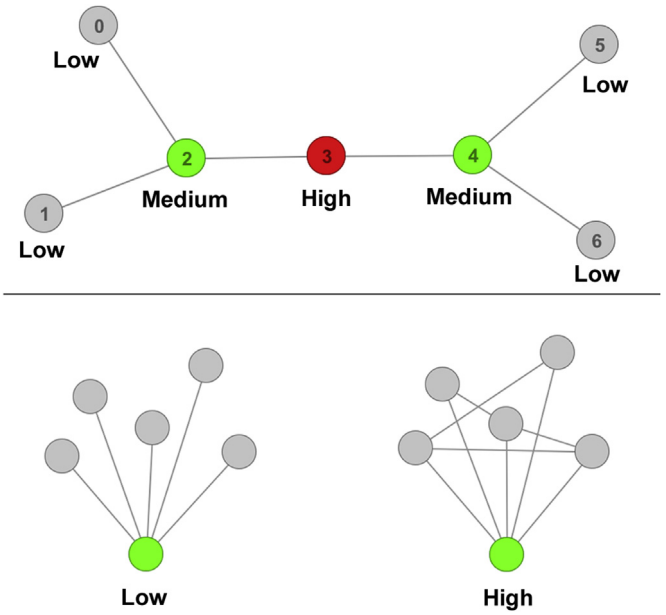

Fig. 1. *Top:* Graphical illustration of betweenness centrality. Betweenness centrality is defined as the proportion of shortest paths of a network that contain a given node. Nodes with low betweenness centrality are colored in gray, nodes with medium betweenness centrality colored in green, and the node with the highest betweenness centrality colored in red. Node 3 (the red node) participates in the highest number of shortest paths between each pair of all other nodes in the network and therefore has the highest betweenness centrality. In the present framework, nodes represent brain regions and edges represent connections between regions. *Bottom:* Graphical illustration of local efficiency. Local efficiency is a measure of ability of a node and its neighbors to transfer information between themselves. The graph on the left has low local efficiency of the green node and its neighbors. The graph on the right has high local efficiency of the green node and its neighbors due to increased connections between the neighbors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Despite the links between the salience network, schizophrenia, and nicotine, little is known about the effects of the drug on salience network connectivity and topology in the illness, particularly in nonsmokers. Filling in this knowledge gap is important as a substantial fraction (~30%) of schizophrenia patients do not smoke (Winterer, 2010). Studying nonsmokers, furthermore, circumvents the unavoidable confounding effects of withdrawal associated with studying a smoking population. The goals of this study, therefore, were to 1) examine the effects of acute nicotine administration (vs. placebo) on connectivity between the three cortical nodes of the salience network (ACC, left and right anterior insula) and the rest of the brain in patients, and 2) examine the effects of nicotine (vs. placebo) on betweenness centrality and local efficiency of the three salience network nodes. We hypothesized abnormal connectivity between the salience network and brain regions associated with other major networks (e.g. the prefrontal cortex/executive network) as well as disrupted betweenness centrality and local efficiency of salience network nodes in patients under placebo administration and amelioration of these differences after nicotine.

2. Materials and methods

2.1. Subjects

36 subjects participated in this study — 17 stable outpatients