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Resting state functional connectivity of the basal nucleus of Meynert in humans: In comparison to the ventral striatum and the effects of age

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ABSTRACT

The basal nucleus of Meynert (BNM) provides the primary cholinergic inputs to the cerebral cortex. Loss of neurons in the BNM is linked to cognitive deficits in Alzheimer's disease and other degenerative conditions. Numerous animal studies described cholinergic and non-cholinergic neuronal responses in the BNM; however, work in humans has been hampered by the difficulty of defining the BNM anatomically. Here, on the basis of a previous study that delineated the BNM of post-mortem human brains in a standard stereotaxic space, we sought to examine functional connectivity of the BNM, as compared to the nucleus accumbens (or ventral striatum, VS), in a large resting state functional magnetic resonance imaging data set. The BNM and VS shared but also showed a distinct pattern of cortical and subcortical connectivity. Compared to the VS, the BNM showed stronger positive connectivity with the putamen, pallidum, thalamus, amygdala and midbrain, as well as the anterior cingulate cortex, supplementary motor area and pre-supplementary motor area, a network of brain regions that respond to salient stimuli and orchestrate motor behavior. In contrast, compared to the BNM, the VS showed stronger positive connectivity with the ventral caudate and medial orbitofrontal cortex, areas implicated in reward processing and motivated behavior. Furthermore, the BNM and VS each showed extensive negative connectivity with visual and lateral prefrontal cortices. Together, the distinct cerebral functional connectivities support the role of the BNM in arousal, saliency responses and cognitive motor control and the VS in reward related behavior. Considering the importance of BNM in age-related cognitive decline, we explored the effects of age on BNM and VS connectivities. BNM connectivity to the visual and somatomotor cortices decreases while connectivity to subcortical structures including the midbrain, thalamus, and pallidum increases with age. These findings of age-related changes of cerebral functional connectivity of the BNM may facilitate research of the neural bases of cognitive decline in health and illness.

Introduction

A prominent feature of the basal forebrain is the collection of large cortically projecting neurons (basal nucleus of Meynert/BNM or magnocellular basal forebrain cell groups) that serve as the primary source of cholinergic input to the entire cortical mantle (Mufson et al., 2003; Raghanti et al., 2011; Selden et al., 1998; Wenk, 1997; Zaborszky et al., 2012, in press). In Alzheimer's and related neurodegenerative diseases, there is a severe loss of cholinergic neurons, and the decrement in cholinergic inputs to the cerebral cortex may underlie cognitive deficits that characterize these age-related conditions (Garibotto et al., 2013). Furthermore, decades of clinical trials showed that medications enhancing cholinergic signals have efficacy in improving cognitive functions in some individuals with Alzheimer's diseases (Doody et al., 2012; Wallace and Bertrand, 2013). Despite its broad involvement in attention, memory, and other cognitive capacities, how the BNM functionally integrates with the rest of the brain is not well understood. This gap of knowledge arises at least in part from the anatomical complexity of the basal forebrain.

The BNM is interdigitated with several anatomical systems in the basal forebrain, including the ventral striopallidal system (ventral pallidum and nucleus accumbens), and cell groups underneath the globus pallidus that bridge the centromedial amygdala to the bed nucleus of the stria terminalis (so-called 'extended amygdala'; Heimer et al., 1991). This complexity has hampered precise anatomical delineation of the BNM. Recently, with cytoarchitectonics of postmortem

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human brains, we presented stereotaxic probabilistic maps of the basal forebrain areas containing the magnocellular cell groups (Zaborszky et al., 2008). On histological sections in ten postmortem brains, the individual compartments of the magnocellular cell groups of the basal forebrain were delineated, 3D reconstructed, and warped to a reference space in Montreal Neurological Institute (MNI) coordinates. The superposition of the cytoarchitectonic maps in the MNI brain shows intersubject variability of the various nuclei and their stereotaxic position relative to other brain structures. Both the right and left BNM showed significantly smaller volumes with increasing age (Zaborszky et al., 2008). This probabilistic map would provide a valuable tool for research of the functions of the BNM in humans that has heretofore been difficult.

Numerous studies have suggested connectivity analysis of resting state fMRI data as a useful alternative to characterizing functional architecture of a brain region. Specifically, low frequency blood oxygenation level dependent (BOLD) signal fluctuations reflect connectivity between functionally related brain regions (Biswal et al., 1995; Fair et al., 2007; Fox and Raichle, 2007). For instance, based on the findings that regions with similar functionality tend to be correlated in their spontaneous BOLD activity, investigators described functional subdivisions of many brain structures including the thalamus (Zhang et al., 2008, 2010), basal ganglia (Barnes et al., 2010), medial superior frontal cortex (Kim et al., 2010; Zhang et al., 2012), anterior cingulate cortex (Margulies et al., 2007), orbitofrontal cortex (Kahnt et al., 2012), cerebellum (O'Reilly et al., 2010), and precuneus (Cauda et al., 2010a,b; Margulies et al., 2009; Zhang and Li, 2012a).

The current study aimed to employ the probabilistic map (Zaborszky et al., 2008) and characterize whole brain functional connectivity of the BNM, as a step to understanding the systems-level functions of this basal forebrain structure in humans. In particular, we compared the functional connectivities of BNM and nucleus accumbens, a ventral striatal structure that is in proximity of the cholinergic space, in the hope of delineating the distinct roles of these two anatomically adjacent structures. In addition to their spatial proximity, both BNM and VS have been implicated in goal-directed behavior (Da Cunha et al., 2012; Grace et al., 2007; Pauli and O'Reilly, 2008; Sarter et al., 2006). In particular, evidence is accruing that the cholinergic and dopaminergic systems may interact to mediate these motivated behaviors (Lester et al., 2010; Mark et al., 2011; Threlfell and Cragg, 2011). For instance, nicotinic receptor blockade or desensitization alters neuronal bursting and dopamine outflow from the VS (Rice and Cragg, 2004). Depletion of cholinergic signals in the ventral striatum resulted in deficits in sensorimotor gating and other cognitive functions (Laplante et al., 2012). Thus, examining the shared and distinct circuits would also further our understanding of the interacting roles of BNM and VS.

Additional goals were to explore the effects of age and gender on the functional connectivities of the BNM and VS. Because the BNM is implicated in age-related cognitive changes, examining age-dependent patterns of BNM connectivity will facilitate research of the neural bases of mild cognitive impairment, Alzheimer's disease and other memory disorders.

Materials and methods

Resting state data

Resting-state fMRI scans were pooled from three data sets (Leiden_2180/Leiden_2200, Newark, and Beijing_Zang, n = 144), downloadable from the 1000 Functional Connectomes Project (Biswal et al., 2010), and our own data (n = 81). In selecting the data, we tried to include as many subjects as possible in order to have more stable findings in the current study, as in our earlier work (Zhang and Li, 2014; Zhang et al., 2012). Thus, we used only datasets acquired under conditions identical to our own datasets (e.g., similar TR, all under 3 T, all eye closed). Individual subjects' images were viewed one by one to ensure that the whole brain was covered. A total of 225 healthy subjects' resting state data (18–53 years of age; 109 men; one scan per participant; duration: 4.5–10 min) were analyzed. Table 1 summarizes these data sets.

Imaging data preprocessing

Brain imaging data were preprocessed using Statistical Parametric Mapping (SPM 8, Wellcome Department of Imaging Neuroscience, University College London, U.K.). Images of each individual subject were first realigned (motion corrected) and corrected for slice timing. Individual structural image was normalized to an MNI (Montreal Neurological Institute) EPI (echo-planar imaging) template with affine registration followed by nonlinear transformation (Ashburner and Friston, 1999, 2005). The normalization parameters determined for the structure volume were then applied to the corresponding functional image volumes for each subject. Finally, the images were smoothed with a Gaussian kernel of 8 mm at Full Width at Half Maximum.

Additional preprocessing was applied to reduce spurious BOLD variances that were unlikely to reflect neuronal activity (Fair et al., 2007; Fox and Raichle, 2007; Fox et al., 2005; Rombouts et al., 2003). The sources of spurious variance were removed through linear regression by including the signal from the ventricular system, white matter, and whole brain, in addition to the six parameters obtained by rigid body head motion correction. First-order derivatives of the whole brain, ventricular and white matter signals were also included in the regression.

Cordes and colleagues suggested that BOLD fluctuations below a frequency of 0.1 Hz contribute to regionally specific BOLD correlations (Cordes et al., 2001). Thus, we applied a temporal band-pass filter ($0.009\ \text{Hz} < f < 0.08\ \text{Hz}$) to the time course in order to obtain low-frequency fluctuations, as in previous studies (Fair et al., 2007; Fox and Raichle, 2007; Fox et al., 2005; Lowe et al., 1998).

Head motion

As extensively investigated in Van Dijk et al., 2012, microhead motion (>0.1 mm) is an important source of spurious correlations in resting state functional connectivity analysis. Therefore, we applied a "scrubbing" method proposed by Power et al. (2012) and successfully applied in previous studies (Power et al., 2012; Smyser et al., 2010; Tomasi and Volkow, 2012a, 2012b) to remove time points affected by head motions. Briefly, for every time point t, we computed the *framewise displacement* given by $FD(t) = |\Delta d_x(t)| + |\Delta d_y(t)| + |\Delta d_z(t)| + r|\alpha(t)| + r|\beta(t)| + r|\gamma(t)|$, where (d_x, d_y, d_z) and (α, β, γ) are the translational and rotational movements, respectively, and r (=50 mm) is a constant that approximates the mean distance between center of MNI space and the cortex and transform rotations into displacements (Power et al., 2012). The second head movement metric was the root mean square variance (DVARS)

Table 1
Demographic information and imaging parameters of the resting-state functional MRI data obtained from the image repository for the 1000 Functional Connectomes Project and our laboratory.

Dataset	Subjects	Ages (years)	Time points	TR (s)	Slice acquisition order
Beijing_Zang	31 M/66 F	18–26	225	2	Interleaved ascending
Leiden_2180	10 M/0 F	20–27	215	2.18	Sequential descending
Leiden_2200	11 M/8 F	18–28	215	2.2	Sequential descending
Newark	9 M/9 F	21–39	135	2	Interleaved ascending
Our own	48 M/33 F	19–53	295	2	Interleaved ascending

Note: M, males; F, females; and TR: repetition time.