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The Limbic and Sensorimotor Pathways of the Human Amygdala: A Structural Connectivity Study

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Abstract—The amygdala plays a key role in gathering social cues to context-appropriate responses that require refined motor behavior, involving either direct or indirect connections with sensorimotor-related areas. Although, several studies investigated the structural and functional limbic connectivity of the amygdala both in animals and in humans, less is known about the limbic modulation on sensorimotor-related areas. However, recent evidences suggest the amygdala as a possible cornerstone in the limbic–motor interface. Herein, we used high-resolution diffusion data of the Massachusetts General Hospital–University of Southern California (MGH–USC) Adult Diffusion Dataset, constrained spherical deconvolution-based signal modeling and probabilistic tractography aimed at identifying and reconstructing the connectivity patterns linking the amygdala to the limbic- and sensorimotor-related areas. As regards the limbic network, our results showed that the amygdala has high probability to be connected with the fusiform gyrus and the lateral orbitofrontal cortex. On the other hand, our connectomic analysis revealed a close interplay between the amygdala and the inferior parietal lobule, followed by the postcentral gyrus, the precentral gyrus and the paracentral lobule. The findings of the present study are in line with previous literature and reinforce the idea of the existence of a limbic–motor interface, which is likely to be involved in the emotional modulation of complex functions such as spatial perception and movement computation. Considering that these pathways may play an important role, not on in physiological conditions, but also in pathological context, further studies should be fostered in order to confirm the existence of a limbic–motor interface and its precise functional meaning.

Key words: complex behaviors, connectome, DWI, emotion, tractography.

INTRODUCTION

The amygdala is a key structure of the limbic system which acts as a hub connecting several subcortical nuclei via the amygdalofugal pathway and stria terminalis. The pivotal role of the amygdala in various aspects of emotional processing and in particular in associating emotive salience to sensorial stimuli is relatively well known (LeDoux, 2012). Recent evidences from patients with neuropsychiatric disorders such as autism, schizophrenia and anxiety disorders (Kleinhans et al., 2008; Grèzes et al., 2009; Baur et al., 2013; Ford et al., 2015; Greening and Mitchell, 2015) led to consider this nuclear complex as a central node of the social brain (Adolphs, 2009; Bickart et al., 2014), integrating complex cognitive functions such as face recognition, social cognition and threatening memories. Therefore, the amygdala can be considered as a key structure gathering social cues to context-appropriate responses that require refined motor behavior, involving either direct or indirect connections with sensorimotor-related areas.

A pioneering study by Mogenson and co-workers deepened the issue of a limbic–motor interface moving from the assumption that emotional drives critically affect action triggering and execution in goal-directed behaviors (Mogenson et al., 1980). Nevertheless, the limbic modulation of complex actions remains widely controversial. A growing body of evidences suggests that the amygdala could be a likely candidate in interconnecting emotion-related and sensorimotor structures, being thus a cornerstone in limbic–motor interface.

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Abbreviations: ASD, Autism Spectrum Disorders; COV, coefficient of variation; CSD, constrained spherical deconvolution; CSF, Cerebral Spinal Fluid; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; fODF, fiber orientations distribution function; HCP, Human Connectome Project; LI, lateralization index; NOS, number of streamlines; OFC, orbitofrontal cortex; ROI, regions of interest.

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Direct connections between the amygdala- and motor-related cortical areas have been investigated in many neuroanatomical studies performed on animals using tract tracing techniques. Projections to supplementary motor area (SMA) have been described in squirrel monkeys using anterograde tracers (Jurgens, 1984). Moreover, connections with anterior cingulate cortex were found in rhesus monkeys (Ghashghaei et al., 2007; Morecraft et al., 2007) and in rats (Sripanidkulchai et al., 1984), while projections to primary motor and sensorimotor cortices were demonstrated in cats (Llamas et al., 1977, 1985; Macchi et al., 1978) and rats (Sripanidkulchai et al., 1984). Finally, amygdala efferents to the lateral premotor cortex have been demonstrated both in rodents and in primates (Avendaño et al., 1983; Amaral and Price, 1984; Llamas et al., 1985; Ghashghaei et al., 2007).

Even though projections from the amygdala- to motor-related areas have been demonstrated in various animal models, less is known about the human analogs of these connections. Functional connectivity studies demonstrated an interplay between the amygdala and motor areas both in healthy subjects and in various types of psychiatric conditions (i.e., phobias, autism, motor conversion disorders) (Åhs et al., 2009; Grèzes et al., 2009; Voon et al., 2011; Qin et al., 2012; Toschi et al., 2017). On the other hand, the physical morphological existence of such connectivity patterns in the human brain is still a matter of debate.

In this regard, using diffusion weighted imaging (DWI) and tractography, it has been recently demonstrated that the basolateral and superficial sub-regions of the amygdala are structurally connected with several motor-related areas (Grèzes et al., 2014).

DWI is a magnetic resonance technique which estimates the diffusion properties of magnetically labeled water (Basser et al., 1994; Henderson, 2012; Le Bihan and Johansen-Berg, 2012) while diffusion tensor imaging (DTI) and tractography allow for the reconstruction of white matter fiber bundles (Cacciola et al., 2016, 2017a,b,c, Milardi et al., 2016a,b, 2017). It is known that DTI suffers from several limitations such as large reconstruction biases and less reliability for crossing, fanning or kinking fibers; (Parker and Alexander, 2005; Behrens et al., 2007; Jones and Cercignani, 2010; Farquharson et al., 2013). Consequently, several sequences and related signal modeling techniques have been recently developed and used for exploring *in vivo* and non-invasively the structural connectivity in the human brain (Parker and Alexander, 2005; Jbabdi and Johansen-Berg, 2011; Farquharson et al., 2013; Jbabdi et al., 2015a). In particular, constrained spherical deconvolution (CSD) is able to reduce reconstruction biases and to provide more robust data, estimating one or more fiber orientations in presence of intravoxel orientational heterogeneity, which is typical of more than 90% of white matter voxels (Tournier et al., 2007, 2008).

Herein, we applied CSD signal modeling on high-resolution diffusion data from 31 healthy subjects of the Human Connectome Project (HCP) aiming at exploring the structural connectivity of the amygdala with limbic- and sensorimotor-related cortical areas, providing a quantitative connectivity analysis of such pathways.

EXPERIMENTAL PROCEDURES

Participants

Thirty-five healthy adults (Males = 19, Females = 16, 20–59 years old) provided in the Massachusetts General Hospital–University of Southern California (MGH–USC) Adult Diffusion Dataset were used for the present study. All subjects gave written informed consent, and the experiments were carried out with approval from the institutional review board of Partners Healthcare. Due to poor brain parcellation results, four participants were excluded from the analysis, that thus were performed on 31 subjects (males = 15, females = 16, age-range 20–59 years).

MRI acquisition and pre-processing

The entire MRI protocol was performed on the 3T CONNECTOM MRI scanner (see (Setsompop et al., 2013) for an overview) housed at the Athinoula A. Martinos Center for Biomedical Imaging at MGH and a custom-made 64-channel phased array head coil was used for signal reception (Keil et al., 2013).

For each participant, the following sequences were acquired:

- 3D T1w-Multi-echo Magnetization-Prepared Rapid Acquisition Gradient Echo (MEMPRAGE): TR 2530 ms, TE 1.15 ms, flip angle 7.0 degrees, FOV 256 × 256 mm^2, band width 651 Hz/Pix, voxel size 1 mm isotropic, acquisition time 6:02 (min:s);
- spin-echo EPI DWI: data were acquired in oblique axial slices with monopolar diffusion gradients and the phase-encoding direction was anterior to posterior (A–P), starting with acquiring a non-weighted diffusion image (b0), and one b0 was collected every 13 DW images thereafter. The following parameters were used: TR 8800 ms, TE 57 ms, FOV 210 × 210 mm^2, echo spacing 0.63 ms, band width 1984 Hz/Pix, slice thickness 1.5 mm, voxel size 1.5 mm isotropic. The diffusion scans were acquired with *b*-value = 3000 s/mm^2 and 64 diffusion directions resulting in an acquisition time of 11:44 (min:s).

Structural T1-MPRAGE scans were corrected for distortion caused by the gradient nonlinearity based on the spherical harmonic coefficients (Jovicich et al., 2006; Glasser et al., 2013) and the facial and ear regions were masked off.

DWIs underwent gradient nonlinearity and motion correction. The b0 images interspersed throughout the diffusion scan were used to estimate the bulk head motions with respect to the initial time point (first b = 0 image), where the rigid transformation was calculated with the boundary-based registration tool in the FreeSurfer package V5.3.0 (Greve and Fischl, 2009). For each b = 0 image, this transformation was then

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