Derivation and Evaluation of Amygdalo-Prefrontal Connections in Humans and Monkeys Using Diffusion Tractography

Longchuan Li[1], Xiaoping Hu[2], Jocelyne Bachevalier[3], Warren Jones[1], Sarah Shultz[1], and Ami Klin[1]

[1]Department of Pediatrics, Marcus Autism Center, Children's HealthCare of Atlanta, Emory University, Atlanta, GA, United States, [2]Department of Biomedical Engineering, Emory University School of Medicine, Atlanta, GA, United States, [3]Yerkes National Primate Research, Emory University, GA, United States

Target audience: Clinical scientists interested in autism, comparative neuroanatomists, MRI engineers

Background: The amygdaloid (Amyg) complex and its connectivity with prefrontal cortical areas comprises a major component of the 'social brain' network and is critical for modeling the pathophysiology of Autism Spectrum Disorders (ASD)[1]. Although extensive studies on Amyg-prefrontal connections have been performed in monkeys using invasive tracers[2,3], research on the related connectivity in humans is largely lacking. Such knowledge is important, as it is a prerequisite for understanding the neural networks in ASD in humans.

Objectives: (1) To derive the Amyg-Prefrontal connections in monkeys using diffusion tractography and compare the results with the anatomical tracing data from the same species; and (2) To examine the corresponding connections in humans using diffusion tractography to determine whether Amyg-Prefrontal connections follow the same pattern as those in monkeys.

Methods: Ten rhesus monkeys and ten humans were included in the study. MRI data were obtained using two 3T Trio Tim scanners. The parameters can be found in [4]. We manually drew Amyg seed masks and prefrontal masks bilaterally in each subject. Fiber-tracking algorithms in FSL were used to trace the connections between the Amyg and the prefrontal cortex. After each subject's Amyg-prefrontal tracts were derived, they were normalized and mapped to volume and surface templates for visualization and comparisons.

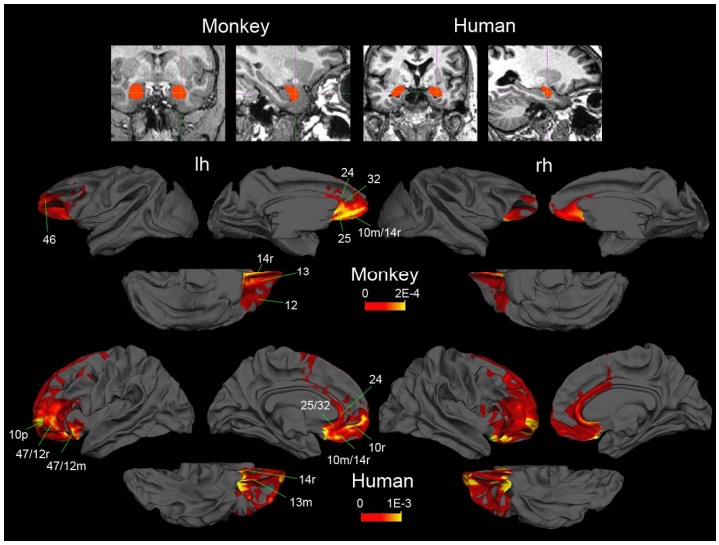

Fig.1 The seed masks in the Amyg and the Amyg-frontal connectivity patterns in monkeys and humans using diffusion tractography. Abbreviations are based on the studies by Ongur [6] and Lewis [7].

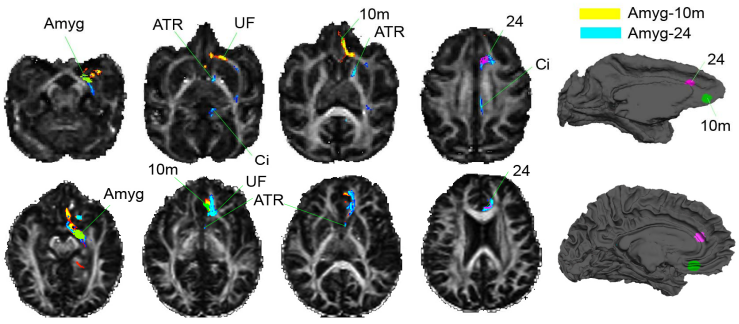

Fig.2 The pathways connecting the amygdala to two ROIs largely corresponding to10m and 24. The ventral pathway connecting to area 10m is color coded as yellow-red while the one connecting to area 24 is blue-lightblue. Abbreviations: Amyg: amygdala, ATR: anterior thalamic radiation, UF: uncinate fasciculus, Ci: cingulum bundle.

Results: Tracing studies in monkeys showed that the heaviest Amyg projections terminated in medial and orbital regions including areas 24, 25, 32, 14, 13 and 12[2,3]. The heaviest prefrontal projections to the Amyg include areas 25, 24, 12o and 13[3]. When comparing our tractography-derived connections in monkeys with tracer literature, we found a good correspondence in the connectivity patterns between the Amyg and the prefrontal cortex[2,3]. We then compared the connectivity between the prefrontal cortex and the Amyg across the species. Connectivity patterns in humans generally showed high resemblance to those in monkeys. Interestingly, a hemispheric asymmetry was noted in both species, with stronger left Amyg-medial prefrontal cortex than to the right, similar as those observed in a tracer study[3]. We then derived the connections between the Amyg and two prefrontal regions-of-interests (ROIs), 10m and 24/32, in one macaque and one human subject to preliminarily examine the trajectories of the connections (Fig.2). There are two most probable pathways connecting area 10m and the Amyg through the medial amygdalofugal pathway and the lateral uncinate fasciculus. The connections between area 24/32 and the Amyg appeared to use somewhat different pathways: in macaques, the two regions are connected through the uncinate fasciculus, the anterior thalamic radiation and the cingulum bundles. In humans, the major pathway first runs rostrally through the uncinate fasciculus and then heads upward through the cingulum bundles to connect to area 24. A less probable pathway is also found via the anterior thalamic radiation.

Conclusions: By combining techniques (tracers vs. diffusion tractography) and species (monkeys vs. humans)[5], we followed a three-stage exploration of connectivity to delineate and validate the Amyg-prefrontal connections in an intensively studied primate species, macaque monkeys, and humans. The next step is to map and validate the major Amyg connections with other cortical lobes using a similar approach and study the relations between the integrity of the obtained amygdala anatomical network and clinical behavioral measures of ASD in humans. Such work may greatly enhance our understandings of the neural underpinnings of ASD.

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