An investigation of the efferent pathways of the amygdala in Major Depressive Disorder using high resolution, multimodal MRI

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Introduction

Embedded deep within the medial temporal lobe of the brain is the amygdala; an almond shaped assembly of nuclei known to be involved in various limbic system processes such as fear, reward, emotional learning and aggression. The underlying neuronal fiber connectivity for the efferent pathways of this structure have yet to be fully delineated with standard neuroimaging.

The aim of my project was:

1. To describe the anatomy of output pathways from this structure in-vivo by employing advanced neuroimaging techniques
2. Elucidate involvement of these pathways in Major Depressive Disorder (MDD)

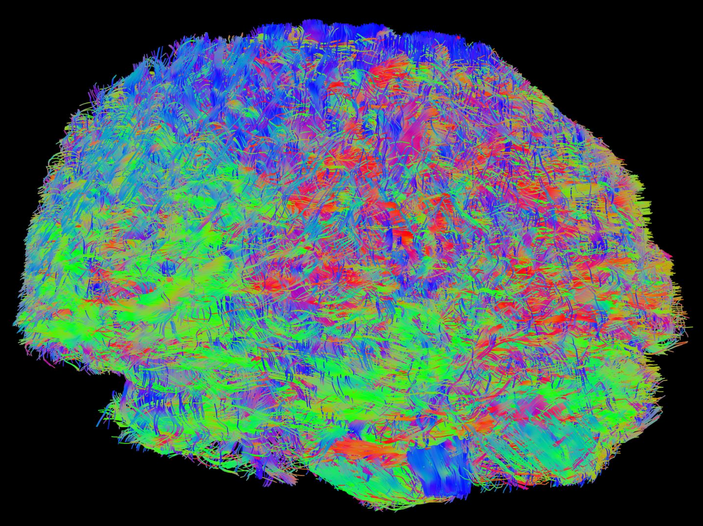

Figure 1: Whole brain tracts, as generated via the Constrained Spherical Deconvolution algorithm

Methods

Diffusion weighted imaging

64 healthy participants were scanned using High Angular Resolution Diffusion Imaging (HARDI) and high-resolution T1 (1mm isotropic) MR imaging at Trinity College Dublin (Phillips, Intega 3T).

Freesurfer 6.0

Three dimensional volumes of the amygdalae and the nucleus accumbens volumes were generated using the automated cortical segmentation protocol with FreeSurfer 6.0 (fig. 2). This protocol of FreeSurfer interrogates contrast differences between substructures using previously defined in-vivo and ex-vivo amygdalae to determine substructure characteristics.

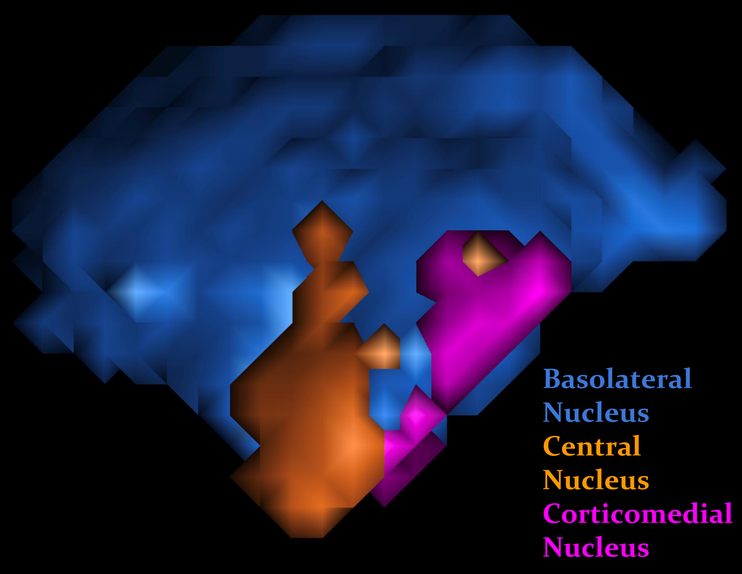

Figure 2: Axial view of nuclear groups within the amygdala, generated using Freesurfer 6.0

DWI Pre-processing

ExploreDTI, a diffusion magnetic imaging toolbox, was utilised for complete pre-processing, modelling and computation of diffusion data. The Constrained Spherical Deconvolution (CSD) algorithm was used to model all potential deterministic streamlines throughout the entire brain (fig. 1).

Tractography

The virtual dissection of the tracts on each hemisphere can be broadly divided into three main steps: tract localization, branch isolation (VAP only) and whole tract integration.

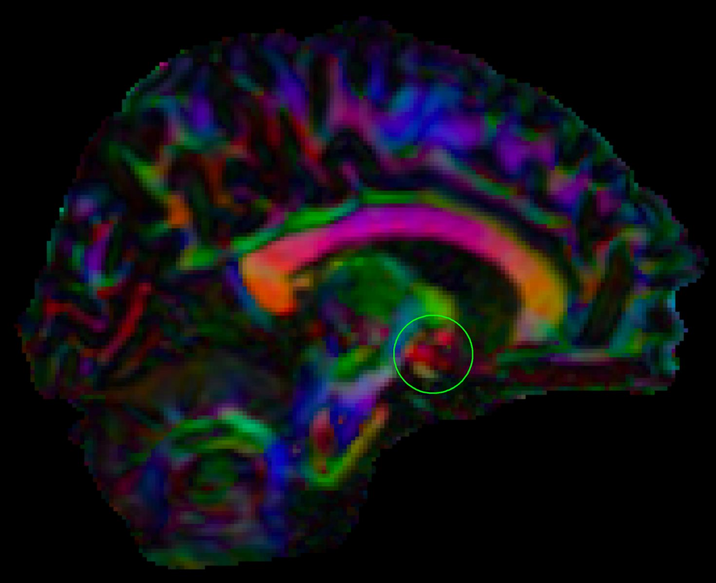

Figure 3: ROI placement on the parasagittal plane of a transformed diffusion weighted image, for isolating the Left VAP

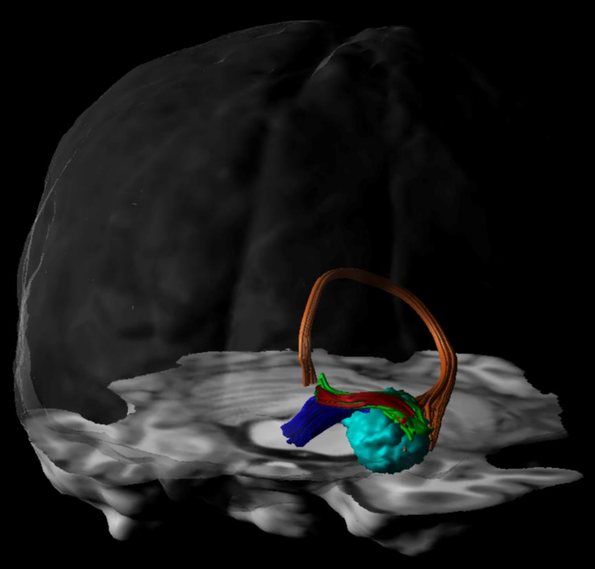

Figure 4: Three dimensional models of the amygdala (cyan), stria terminalis (brown) and the branches of the VAP which extends to the hypothalamus (green), nucleus accumbens (dark red) and basal forebrain (blue). White arrows point at the hypothalamic region.

Results

The bilateral stria terminalis, ventral amygdalofugal pathway and the anterior commissure were all isolated using tractography. Each tract was segmented for consistent spatial containment.

The VAP could reliably and consistently be virtually dissected in all participants. Branches which pass through the hypothalamus, basal forebrain and nucleus accumbens were delineated consistently in the whole sample by the raters (fig. 4). The branches which serve the mediodorsal thalamus and brainstem were found inconsistently.

Fractional Anisotropy was smaller in the depressed cohort of the left stria terminalis (table 1). Along tract analysis elucidated that posterior aspects of the tract were driving these effects (table 2).

The data analysis comparing the anterior commissure and ventral amygdalofugal pathway between healthy controls and depressed participants has yet to be completed. This remained unfinished due to inaccessibility of the lab during the COVID-19 pandemic.

	p value	F stat	Partial eta^2
Number of tracts	0.117	2.502	0.026
Approximate Volume	0.78	0.078	0.001
Fractional Anisotropy	**0.002**	9.701	0.095
Mean Diffusivity	0.622	0.244	0.003
Axial Diffusivity	0.387	0.755	0.008
Radial Diffusivity	0.167	1.938	0.021

Table 1: ANCOVA of metrics in the left stria terminalis comparing healthy and depressed participants while controlling for age, sex and eTIV.

	Left			Right		
Segment	F	Sig.	Eta^2	F	Sig.	Eta^2
1	0.75	0.389	0.008	0.673	0.414	0.007
2	4.075	0.046	0.042	2.519	0.116	0.027
3	5.5	0.021	0.056	0.659	0.419	0.007
4	6.756	0.011	0.068	0.427	0.515	0.005
5	7.559	0.007	0.076	1.096	0.298	0.012
6	7.489	0.007	0.075	0.762	0.385	0.008
7	10.277	0.002	0.1	1.207	0.275	0.013
8	8.339	0.005	0.083	1.708	0.194	0.018
9	6.729	0.011	0.068	2.061	0.154	0.022
10	8.436	0.005	0.084	0.251	0.617	0.003
11	8.252	0.005	0.082	0.295	0.588	0.003
12	6.468	0.013	0.066	0.442	0.508	0.005
13	5.573	0.02	0.057	1.844	0.178	0.02
14	5.026	0.027	0.052	3.317	0.072	0.035
15	5.487	0.021	0.056	2.129	0.148	0.023
16	5.304	0.024	0.055	1.465	0.229	0.016
17	2.75	0.101	0.029	1.548	0.217	0.017
18	4.499	0.037	0.047	1.109	0.295	0.012
19	3.094	0.082	0.033	0.08	0.778	0.001
20	1.964	0.164	0.021	0.262	0.61	0.003
21	1.363	0.246	0.015	1.23	0.27	0.013
22	4.33	0.04	0.045	0.188	0.665	0.002
23	3.522	0.064	0.037	0.829	0.365	0.009
24	4.432	0.038	0.046	0.392	0.533	0.004
25	2.965	0.088	0.031	0.478	0.491	0.005
26	0.444	0.507	0.005	3.242	0.075	0.034
27	0.121	0.729	0.001	0.9	0.345	0.01
28	0	0.988	0	0.226	0.635	0.002
29	0.372	0.543	0.004	0.022	0.881	0

Table 2: Multiple ANCOVAs of segments of the stria terminalis comparing fractional anisotropies of healthy and depressed participants while controlling for age, sex and eTIV.

Conclusion

Our protocols for manual isolation using tractography of the stria terminalis and ventral amygdalofugal pathway (with branches) are novel and may also open avenues for identification of pathologies within components of these enigmatic bundles in other neuropsychiatric conditions such as schizophrenia, anxiety disorders etc.

Fractional anisotropy was smaller in the posterior left stria terminalis of depressed participants. This project is incomplete for the other two pathways due to restrictions from the pandemic.

References:

1. Richardson JS. The amygdala: historical and functional analysis. Acta Neurobiol. Exp. 1973 Jan 1;33(5):623-48.
2. Mori S, Kageyama Y, Hou Z, Aggarwal M, Patel J, Brown T, Miller MI, Wu D, Troncoso JC. Elucidation of white matter tracts of the human amygdala by detailed comparison between high-resolution postmortem magnetic resonance imaging and histology. Frontiers in neuroanatomy. 2017 Mar 14;11:16.