Can the Cingulum get you down? A comparative study of cingula changes and their involvement in Major Depressive Disorder Pathophysiology

Alannah Grealy[1,2], Elena Roman[1] , Hannah Schwartz[1], Marissa Malkit[1], Anurag Nasa[1], Veronica O'Keane[1], Erik O'Hanlon[1], Darren William Roddy[1]

[1]Trinity College Institute of Neuroscience, [2]Laidlaw Foundation Programme

INTRODUCTION

The cingulum bundle, one of the largest white matter fiber tracts of the brain at 5-7cm in diameter (1) and present bilaterally, is a major structure of the limbic system. Extending from the subgenual cingulate cortex (BA25) through to the amygdala (2), it communicates with frontal, parietal and medial temporal cortices. It is a key structure in the Papez circuit and as such is essential for the development of cognitive and emotional skills through adolescence and beyond.

Major Depressive Disorder (MDD) is a multifactorial disease which can manifest through biological, psychological and social means. However, the exact neurobiological mechanisms that translate into particular depressive symptomatology have largely remained elusive. No study has of yet coherently determined development and maturation of the cingulum bundle as well as pathological variants of this process in the human brain. While some research has touched on the area, there has not been any novel developments to date on the role of the cingulum in depression.

Therefore the goal of this investigation was to determine FA changes in 50 patients with MDD aged 15-65 through segmentation of the cingulum bundle in diffusion MRI following previously described protocol by Jones et al 2013, and to compare these results with 51 control patients within the same age range.

METHODS

51 consenting adults, 25 of which were female with no declared illnesses were scanned using a High Angular Radial Diffusion Imaging (HARDI) protocol. This process was then repeated with 50 patients with a diagnosis of major depressive disorder. All participants were recruited as part of the REDEEM group in Trinity College Dublin. Following constrained spherical deconvolution whole brain tractography, the cingulum bundle was reconstructed.

A boolean logic based protocol was implemented to virtually dissect the cingula. This involved dividing the cingulum bundle into 4 distinct anatomico-functional segments (subgenual, body, retrosplenial and parahippocampal). A total of 5 regions of interest (ROIs) were utilised to reconstruct these different divisions. ROIs were placed following the previously described protocol by Jones et al 2013 (3).

Following ROI placement, the regions were segmented using the ExploreDTI tool and tracts inconsistent with cingula anatomy were removed. Macroscopic and microscopic data from these virtually dissected cingula analogues were then extrapolated and statistically examined using IBM SPSS Statistics 26. Ethical approval for this investigation came under the remit of the REDEEM study at Trinity College Dublin.

		Control	Depressed	Total
Gender	Male	25	17	42
	Female	26	31	57
	Total	51	48	99
Handedness		51 Right, 0 Left	47 Right, 1 Left	98 Right, 1 Left
Age		30.04341 ± 12.6533	30.44098 ± 11.1829	30.23617 ± 11.90391
HAM-D		1.02 ± 1.46371	22.6875 ± 4.23338	11.6327 ± 11.32681
Duration of Illness		N/A	29.4896 ± 70.33366	29.4896 ± 70.33366

Table 1. Demographics

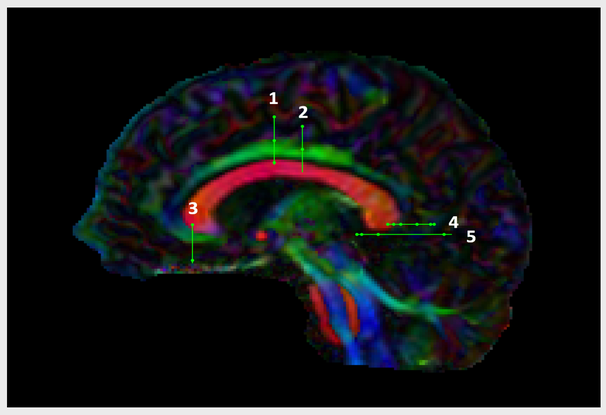

Figure 1. Region of Interest placements 1-5

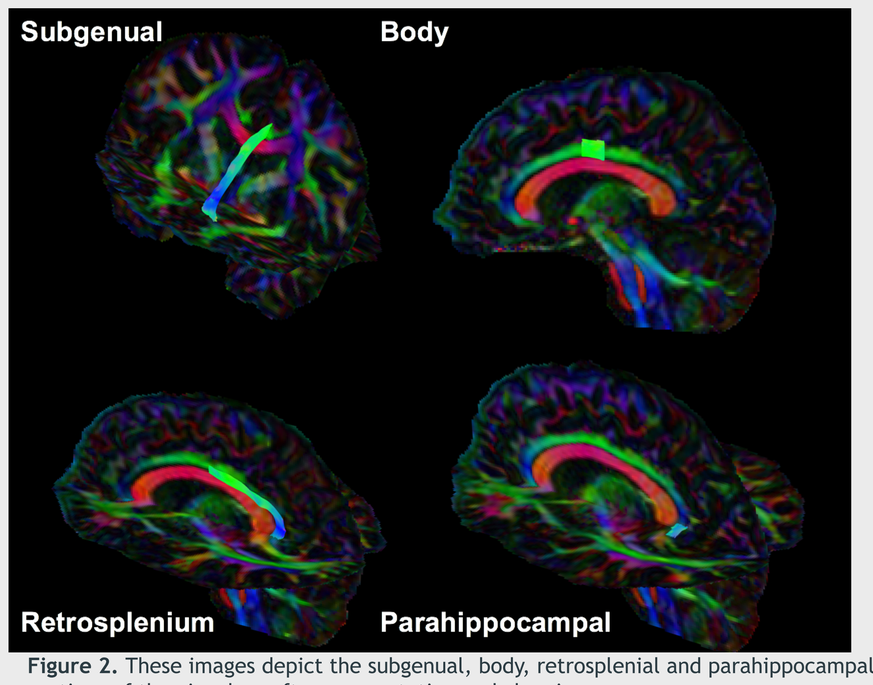

Figure 2. These images depict the subgenual, body, retrosplenial and parahippocampal sections of the cingulum after segmentation and cleaning.

		Subgenual		Body		Retrosplenial		Parahippocampal	
		Effect direction	p, F, eta^2	Effect direction	p, F, eta^2	Effect direction	p, F, eta^2	Effect direction	p, F, eta^2
Left	Fractional Anisotrophy	ns	0.1066261378, 2.654, 0.027	ns	0.269586491, 1.233, 0.013	ns	0.1139747602, 2.545, 0.026	<	0.0032203016, 9.142, 0.089
	Mean diffusivity ([λ1 + λ2 + λ3]/3)	>	**0.0002127617, 14.85, 0.136**	>	**0.0000004498, 29.426, 0.238**	>	**0.0000000158, 38.295, 0.289**	>	**0.0000405082, 18.557, 0.165**
	Axial diffusivity (λ1)	ns	0.5748242764, 0.317, 0.003	>	0.0235443716, 5.299, 0.053	>	0.0062071827, 7.839, 0.077	ns	0.5998803088, 0.277, 0.003
	Radial diffusivity ([λ2 + λ3]/2)	>	0.0093128366, 7.049, 0.07	>	0.0027099984, 9.49, 0.092	>	**0.0012517917, 11.072, 0.105**	>	**0.0000469733, 18.22, 0.162**
Right	Fractional Anisotrophy	ns	0.5041281303, 0.45, 0.005	ns	0.368955713, 0.815, 0.009	<	0.0461711737, 4.083, 0.042	<	0.0219285109, 5.43, 0.055
	Mean diffusivity ([λ1 + λ2 + λ3]/3)	>	0.0058020902, 7.971, 0.078	>	**0.0000019258, 25.785, 0.215**	>	**0.0000000043, 41.903, 0.308**	>	**0.0013828142, 10.866, 0.104**
	Axial diffusivity (λ1)	ns	0.1601276752, 2.005, 0.021	>	0.0229173934, 5.349, 0.054	>	0.017431428, 5.858, 0.059	ns	0.7302149546, 0.12, 0.001
	Radial diffusivity (λ2 + λ3)/2)	ns	0.0878275482, 2.975, 0.031	>	0.0072800075, 7.527, 0.074	>	**0.000006127, 22.976, 0.196**	>	**0.0018073431, 10.315, 0.099**

Table 2. This table describes the findings from analyses of covariance (ANCOVA), controlling for age, gender and estimated total intracranial volume (eTIV). The effect direction expresses whether the metric was increased (>), decreased (<) or not-significant (ns) in patients with depression. The p value, F value and partial eta^2 effect size are also provided. For all these analyses: df1=1, df2=97. Based on a F distribution table with α = 0.05, the critical F statistic is 3.9391; for the Bonferroni adjusted α = 0.002, the critical F statistic is 10.08

RESULTS

- A total of 99 participants were used for the purposes of this investigation, 42 male and 57 female. Two participants were excluded following issues related to COVID-19.
- 48 participants had a clinical diagnosis of MDD, comprising the depressed cohort of this study. Of the depressed cohort, 8 participants had a medical history of recurrent episodes of depression while 40 participants were included following first-time presentation.
- 51 participants with no underlying medical conditions were used as control subjects.
- The mean duration of illness within the depressed cohort was 29.490 months with a standard deviation of 70.334 months.
- There was a statistically significant increase in Mean Diffusivity (MD) bilaterally across all 4 regions of the cingulum bundle in the depressed cohort compared to the non-depressed cohort, with a corresponding statistically significant decrease in Fractional Anisotropy (FA) in both the right retrosplenial and bilateral parahippocampal regions.
- An increase in Axial Diffusivity (AD) was observed in both body and retrosplenial regions.
- Radial Diffusivity (RD) was found to be statistically significant in retrosplenial and parahippocampal regions where there was an increase in RD among the depressed cohort compared to the non-depressed.

SIGNIFICANCE

- While previous research has implicated the anterior cingulate cortex with MDD, our data suggests the potential involvement of the posterior cingulate cortex as well.
- The results of our data depict areas of change all along the cingulum bundle which may be due to decreased axonal density and packing, increased multiple cross fibre orientations or less likely, demyelination processes. To determine the exact causes of these changes in cingula anatomy, we intend to further interrogate our data with more in-depth analyses.
- The results of this investigation indicate the potential of the cingulum bundle to be used as a biomarker in MDD pathophysiology in future.

SYNOPSIS FOR THE NON-SPECIALIST

In summary, this investigation looked at differences between a prominent white matter tract in the brain known as the cingulum bundle in depressed and non depressed individuals using various neuroimaging techniques. Information gathered was measured and analysed using four different methods of measurement that interrogate the diffusion properties of water molecules. The results of this investigation show that there are changes along the entirety of the cingulum bundle in depressed individuals, which may be caused by a number of factors. It will be possible to uncover the exact cause of these changes through further statistical analysis. The results of this investigation indicate that the cingulum bundle may be used to track disease progression and response to therapy in MDD in future.

References:

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