

# Cingulum bundle asymmetry predicts trait neuroticism: A DTI study

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## Introduction

Amygdala and subgenual cingulate have been linked with anxiety and mood disorders, for which the trait neuroticism is a risk factor. Neuroticism has been negatively associated with right amygdala grey matter concentration<sup>1</sup>. Moreover, functional connectivity between amygdala and subgenual cingulate predicts the anxiety and depression related personality trait harm avoidance<sup>2</sup>. Larger right anterior cingulate surface has been correlated with higher harm avoidance scores<sup>3</sup>. Reduced left subgenual cingulate grey matter volume has been found in bipolar and unipolar depressives<sup>4</sup>. An altered balance between left and right subgenual cingulate function has been hypothesized to contribute to heightened affective, neuroendocrine, and sympathetic autonomic arousal observed in depression<sup>5</sup>. The major fibre bundle connecting anterior cingulate and amygdala, hippocampus and hypothalamus is the cingulum. Here we report associations between neuroticism and cingulum white matter microstructure in healthy adults. The major hypothesis was that neuroticism, adjusted for age and gender, would be associated with fractional anisotropy (FA) in left and right cingulum, possibly reflected in the extent of laterality. The secondary hypothesis was that such relationship might also be observed for the uncinate fasciculus. Parallel ( $\lambda_{\parallel}$ ) and perpendicular ( $\lambda_{\perp}$ ) diffusivities were studied to further explore observed effects.

## Materials and Methods

Forty-five healthy adults (14 females, 31 males) aged 20-82 (37.5±20.5) were included in the study. Neuroticism, which consists of six subscores (facets), was assessed using the Danish version of the 240-item self-report Revised NEO Personality Inventory (NEO-PI-R)<sup>6</sup>. Diffusion-weighted images were acquired in 61 directions (b=1200 s/mm<sup>2</sup>) using a 3T MR-scanner. The diffusion tensor was fitted using the RESTORE algorithm implemented in Camino to derive FA,  $\lambda_{\parallel}$  and  $\lambda_{\perp}$ . Tract-based spatial statistics (TBSS<sup>7</sup>, part of FSL) analysis was conducted, in which all subjects' FA or diffusivity data are projected onto a mean tract skeleton, representing the centres of all tracts common to the group. ROIs were drawn in the right and left cingulum and uncinate fasciculus. Mean FA and diffusivity values were extracted from all four ROIs for each subject for statistical analyses. The laterality index (LI) = (2\*(Left - Right) / (Left + Right)) of the cingulum was calculated for FA,  $\lambda_{\parallel}$  and  $\lambda_{\perp}$  and used in multiple linear regression models predicting neuroticism. Post hoc analyses were conducted to explore which neuroticism subscales contributed to observed effects.

## Results

Multiple linear regression models showed that neither left ( $r^2 = 0.15$ ,  $\beta = -0.102$ ,  $p = 0.56$ ), nor right ( $r^2 = 0.15$ ,  $\beta = 0.13$ ,  $p = 0.45$ ) cingulum FA, adjusted for age and gender, were significantly associated with neuroticism. However, cingulum FA LI, adjusted for age and gender, significantly predicted neuroticism ( $r^2 = 0.269$ ,  $\beta = -0.372$ ,  $p = 0.01$ , Fig. 1). Note that left cingulum FA was significantly higher than right cingulum FA ( $p < 0.0001$ ). When exploring the diffusivities, cingulum  $\lambda_{\perp}$  LI ( $r^2 = 0.25$ ,  $\beta = 0.346$ ,  $p = 0.02$ ), but not cingulum  $\lambda_{\parallel}$  LI ( $p = 0.46$ ), adjusted for age and gender, was significantly associated with neuroticism. No significant effects were observed for the uncinate fasciculus FA ( $p > 0.49$ ). Results from post hoc analysis of associations between cingulum FA LI and neuroticism subscales are summarized in the Table.

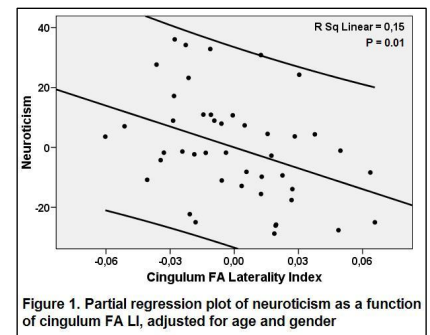


Figure 1. Partial regression plot of neuroticism as a function of cingulum FA LI, adjusted for age and gender

## Discussion/Conclusion

The results suggest that diminished left-right asymmetry in cingulum FA (higher in right relative to left) is associated with higher neuroticism scores after adjusting for age and gender effects. The association was mainly driven by variability in cingulum  $\lambda_{\perp}$ . Post hoc analysis revealed that the facets anxiety, angry hostility, depression and vulnerability were the main contributors to the observed associations. All these facets have previously been linked to major depression and anxiety disorders<sup>8</sup>. One might speculate whether cingulum FA and  $\lambda_{\perp}$  asymmetries are possible markers of increased risk of developing anxiety and mood disorders. Future studies are necessary to address this question.

## Acknowledgments

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## References

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**Table 1.** Post hoc analysis: Multiple linear regression models predicting the six neuroticism subscales

	R <sup>2</sup>	Cingulum FA LI		Age		Gender	
		$\beta$	P	$\beta$	P	$\beta$	P
<b>Neuroticism (N)</b>	0.269	-0.372	0.010	-0.326	0.026	0.294	0.042
<b>Anxiety</b>	0.204	-0.301	0.043	-0.280	0.063	0.284	0.058
<b>Angry hostility</b>	0.164	-0.308	0.044	-0.337	0.030	-0.026	0.865
<b>Depression</b>	0.216	-0.307	0.038	-0.106	0.469	0.323	0.031
<b>Self-consciousness</b>	0.112	-0.192	0.214	-0.296	0.063	0.158	0.310
<b>Impulsiveness</b>	0.138	-0.076	0.616	-0.353	0.026	0.238	0.125
<b>Vulnerability</b>	0.210	-0.356	0.017	-0.095	0.521	0.259	0.082