

# Structural connectivity analysis in treatment-resistant depression

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Depressive disorder is characterized by a profound dysregulation of affect and mood as well as additional abnormalities including cognitive dysfunction, insomnia, fatigue and emotional disturbance. Converging evidence shows that a dysfunction in prefrontal-subcortical circuits is associated with depressive state. However, the process of treatment resistance was poorly studied. One study of functional magnetic resonance imaging has reported more disrupted connectivity in prefrontal areas and in thalamus for resistant (R) group (Lui et al., 2011). These observations suggest a modification of functional connectivity in the prefrontal-subcortical circuits in the R patients. Using graph theory-based analysis, we examined white matter changes in the organization of networks in R patients compared with non-resistant (NR) group.

LONGIDEP is prospective longitudinal study of patients suffering from mood depressive disorder. Diffusion tensor imaging (DTI) scans were acquired with 30 directions using an EPI sequence at a b-value of 1000s/mm<sup>2</sup>. T1 images were collected for volume measurements. Using a clinical global impression-improvement score at the 6 months assessment (Min et al., 2012), the population sample was divided into two groups of 28 R and 26 NR patients. The DTI data were processed with the open source medical image processing toolbox Anima (<https://github.com/Inria-Visages/Anima-Public/wiki>), including skull stripping, eddy current correction, denoising, followed by fiber assignment by continuous tracking method (Wiest-Daesslé et al., 1999). To define the graph nodes of the connectivity matrix, Freesurfer analysis (Dale et al., 1999) was used to parcellate cortical and subcortical gray matter into a total of 80 regions of interest (ROI). Then, a connectivity matrix for each subject with each element depicting the number of fibers that passes through a pair of ROIs, normalized by the mean volume of the two ROIs, was created. After adjusting for gender, disease duration and medication load, a two-sample Student t-test was performed and combined with a permutation test.

We revealed 15 areas with significant density differences in R patients compared to NR subjects (figure 1). Reduced fiber density was observed bilaterally between frontal cortex and caudate in R patients. We also observed reduced interhemispheric fibers in the prefrontal and frontal lobes for patients with pejorative outcome. However, increased connectivity was observed in some cerebral regions such as in anterior cingulate cortex (ACC) and inferior frontal cortex, as well as in insula, amygdala and postcentral gyrus for NR groups compared with R patients.

Our diffusion imaging data showed significant differences of fiber density between patients suffering from resistant and nonresistant depression. The NR depression seems associated with decreased connectivity among distributed limbic areas, particularly in the ACC and in basal ganglia. However, the R patients exhibit a reduced connectivity in anterior limb of internal capsule and genu of corpus callosum compared with NR patients. Combined with previous studies, which described a widespread disruption in prefrontal-subcortical networks, this result suggests a more important connectivity decrease in the frontal cortex, as well as a smaller reduction in the limbic circuit for the patients with pejorative outcome. These results were consistent with connectivity studies (Lui et al., 2011; Coloigner et al., 2018), which suggested that the degree of disruption could influence the resistance severity and that two distinct networks could be implicated in NR and R depression.

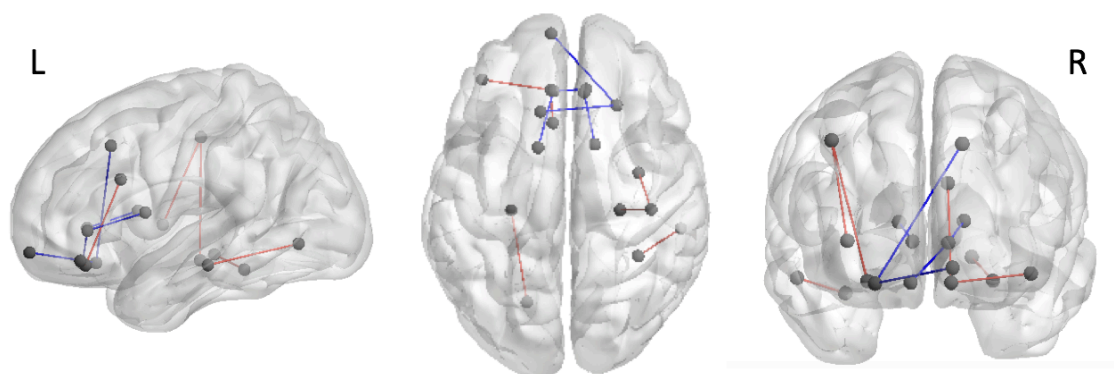


Figure 1: Graphical representation of the connections with significant difference in term of fiber density between patients suffering from resistant and nonresistant depression.

## References

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