TITLE: A Voxel-Based Diffusion Tensor Imaging Study in unipolar and bipolar depression

AUTHORS: Repple, Jonathan; Meinert, Susanne; Grotegerd, Dominik; Kugel, Harald; Redlich, Ronny; Dohm, Katharina; Zaremba, Dario; Opel, Nils; Buerger, Christian; Foerster, Katharina; Arolt, Volker; Heindel, Walter; Deppe, Michael; Dannlowski, Udo

ABSTRACT: The absence of neurobiological diagnostic markers of bipolar disorder (BD) leads to its frequent misdiagnosis as unipolar depression (UD). We investigated if changes in fractional anisotropy (FA) could help to differentiate BD from UD in the state of depression.

Using Diffusion Tensor Imaging (DTI) we employed a voxel-based analysis approach to examine Fractional Anisotropy (FA) in N=86 patients suffering from an acute major depressive episode according to DSM-IV (N=39 BD, N=43 UD), and N=42 healthy controls (HC). The groups did not differ in sex, age or total education time. For comparability reasons with previous studies, a stepwise approach was chosen, investigating FA differences 1. Across the entire brain (including gray matter) 2. Restricted to white matter (FA >.2), and 3. Hypothesis driven anatomically defined tracts (ROI analysis).

Whole-brain analyses revealed decreased FA in the left middle frontal gyrus and in the right inferior frontal gyrus in UD versus HC, in the left superior medial gyrus in BD versus HC. A restriction to white matter further showed decreased FA in the right corticospinal tract in UD versus HC and in the right corticospinal tract/superior longitudinal fascicle in BD versus HC and also in BD versus UD. Finally, region of interest analysis revealed decreased FA in BD versus UD in the corpus callosum and in the cingulum.

This is one of very few studies directly showing differences in FA between BD and UD. Gray matter FA changes in prefrontal areas might be precursors for future prefrontal GM abnormalities in these disorders.

Very well-written manuscript focusing on the differences in fractional anisotropy in gray matter, white matter and ROIs in BD and UDs. I have few minor comments that should be easily addressed by the authors and will make this paper stronger.

1. Page 10. Please provide the direction of the correlations (negative/positive)
2. Did you compare the strength of the coefficients of correlations between groups? for instance whether the correlation between number of depressive episodes and FA in the sup medial gyrus was stronger in BD than in UDs? I also noticed that correlations were overall positive for UDs and negative for BDs. All these questions should be addressed and could be an interesting topic for discussion in the conclusions.
3. Why didn’t you include healthy individuals in your study? please address this somewhere in the manuscript
4. Based on the age of your participants and mean age of onset of symptoms I estimate that that age of onset of UD/BDs ranged from approximately 15 to 39 years. I think the authors should mention this point to highlight for instance that their results may apply to early to late onset UD/BDs. Overall a comment on the effects of the disorders on the brain in possibly critical developmental periods could be mentioned.
5. Did these participants have comorbidities? If so they should be at the very least listed in the table and possibly discussed if relevant.
6. Did the authors collect measures of global functioning or cognitive measures such as memory? if not this could be discussed or included as a future direction.

Minor details

1. in the abstract please provide ages of the groups.
2. Page 10. Please correct “DTI measures..”
3. Please provide references in the last paragraph of page 10 where you explain how the reported anatomical connections are important for emotional dysregulation etc.