ABSTRACT: Objectives  
Bipolar disorder (BP) is a debilitating psychiatric disease that is not well understood.  
Previous diffusion MRI (dMRI) studies of BP patients found prominent microstructural white  
matter (WM) abnormalities of reduced fractional anisotropy (FA). Because FA is a nonspecific  
measure, relating these abnormalities to a specific pathology is difficult. Here, dMRI specificity is  
increased by Free Water Imaging, which allows for identification of changes in extracellular  
space (Free Water (FW)) from neuronal tissue (fractional anisotropy of tissue (FA-t)). Previous  
studies identified increased FW in early schizophrenia (SZ) stages which was not present in chronic stages. Similar analyses in BP will allow for a comparison  
between disorders.  
Methods  
3T DWI data was acquired for 17 chronic BP and 28 healthy control (HC) participants at  
Oxford University. Tract Based Spatial Statistics was utilized to generate a WM skeleton. Free  
Water Imaging deconstructed the diffusion signal into extracellular FW and tissue FA-t maps.  
These maps were projected onto the skeleton and FA, FA-t, and FW were compared between  
groups.  
Results  
We found significantly lower FA in patients with BP when compared to HC in areas that  
overlapped with extensive FW increases. There was no difference in FA-t.  
Conclusions  
Our study suggests that chronic BP shows similar WM changes to early SZ stages,  
implicating that extracellular FW increases could be a transient indication of recent psychotic  
episodes. Since FW increase in SZ has been suggested to be related to neuroinflammation, we  
theorize that neuroinflammation might be shared between chronic BP and early SZ.

Review

Novel research work that goes beyond the conventional single tensor diffusion analyses and uses free water imaging to separate changes in extracellular space from neuronal tissue. Another novel point is the use of FW in BD as this methods has previously (and successfully) been applied to populations with psychosis and depression. I am overall impressed with the quality of the methodology section, and description of the rationale and aims of the study. I have few comments that, I believe, should be easy to address.

1. Please add a few more details on the relevance of FA-t. What would a high or low FA-t mean?
2. Since you entered motion parameters into your models wouldn’t the motion artifacts mentioned in the conclusions somewhat corrected for? Could you please clarify?
3. Also, in your conclusions, please clarify further what the lack of FA-t differences, along with the lack of correlations with the PANSS?
4. Could you please comment on changes in FA, FW, FA-t with current mood status, e.g. what about severity of manic symptoms vs depressive symptoms?
5. In your discussion please try to highlight the relevance of the regions showing differences in FA. How do they relate to the classical 1.clinical and 2.neuropsychological presentation of BD patients?
6. Also, would there by any tract or area of the brain that could show FA or FW alterations even if there are none? e.g. false positives. It would be good to highlight the strength or limitation of FW in regard to this too.
7. Table 1. Please provide additional information on current mood state, age of onset, number of hospitalizations, medication (e.g. type of medication),ethnicity, education, full scale IQ, number of mood episodes, illness duration.
8. Figure. Please provide an understandable label and units of measurement for both X and Y axis and explain the FW acronym in your caption. The rule of thumb is that the caption should help the reader understand the significance of a figure without reading the main text. The structure of a caption should include a short title and short descriptions of what the main “take-home” message of the figure.