Links between white matter integrity, eye movement function, and health in postconcussion syndrome

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Introduction

Postconcussion syndrome (PCS) can affect up to 20-30% of patients with mild closed head injury (mCHI), comprising the prolonged and disabling persistence of postconcussional symptoms. Previous studies [1,2] have identified eye movement function at 1 week post-injury as a possible predictive marker for PCS, showing that mCHI patients who later develop PCS manifest measurable differences in eye movement function compared to mCHI patients of similar injury status who later show a good recovery. This study examined the relationship of oculomotor function with structural brain integrity as measured by diffusion tensor imaging (DTI) at 1 week after mCHI. The study focused on the contrast between patients who later (i.e., at 3 months post-injury) met the diagnostic criteria for PCS and patients with good recovery. This is the first study to examine the relationship between eye movement function and imaging evidence of brain injury in the context of eye movement control after mCHI.

Methods

Participants – The study included 20 participants with mCHI (Glasgow Coma Scale score 13-15). Post-traumatic amnesia was present in 17 patients, ranging between 3 min and 4 h (mean = 68 min) and 11 patients had a confirmed loss of consciousness (mean = 4.95 min, range 0.5–15 min). Mean age was 37.3 years (SD 11.3, range 16–50 years) and mean years of education was 14.7 (SD 2.58, range 11–18 years). Mean time post-injury was 6.3 days (SD 2.6, range 3-11). Follow-up at 3 months (mean 89 days) determined level of recovery and incidence of PCS (adapted WHO criteria) via health status questionnaires (SF-36 Health Survey v2, Rivermead Postconcussion Symptoms Questionnaire, Rivermead Head Injury Follow-up Questionnaire, Hospital Anxiety & Depression Scale - HADS) [3].

Figure 1 – SMI eye tracker

Eye movements were recorded using an SMI iViewX eye tracker (Fig. 1) including paradigms for reflexive saccades, antisaccades, memory-guided sequences, self-paced saccades, predictive saccades, as well as sine and random oculomotor smooth pursuit [3]. Key measures were saccade latency (ms), saccade velocity (°/s), saccade duration (ms), number of self-paced, saccades within 30 s, mean absolute position error of the final eye position, and gain (eye position/stimulus position) of the primary saccade and final eye position. Key measures for oculomotor smooth pursuit were the average eye peak velocity (°/s) after removal of all saccades from the tracking performance, tracking lag (ms), number of catch-up saccades, and mean absolute tracking error (MAE) (deg).

DTI was acquired (median +1 day of oculomotor assessment) on a 3T GE HDx scanner using a 2D diffusion-weighted spin echo EPI sequence (TE=75.5ms, TR=13s) with diffusion weighting in 28 uniformly distributed directions ($b=1000s/mm^2$) and four acquisitions without diffusion weighting. DTI data were analysed in ExploreDTI [4] including correction of subject motion and eddy-current induced geometrical distortions, calculation of diffusion tensors, fractional anisotropy (FA) and mean diffusivity via a weighted-linear regression procedure, and coregistration to MNI space. Standard deterministic streamline tractography [5] was used to reconstruct fiber pathways using brain atlases (Juelich and JHU) [6].

Data analysis – Discriminant function analysis identified eye movement disparities between the prospective PCS- and non-PCS groups. Stepwise-forward multiple linear regression analysis was used to examine the relationship of FA and diffusivity in atlas-defined brain regions with (a) oculomotor function and (b) measures of health status. Separate analyses were conducted for the JHU and the Juelich atlas. In-model variables were limited to 10 in the discriminant function analyses and to 6 in the regression analyses.

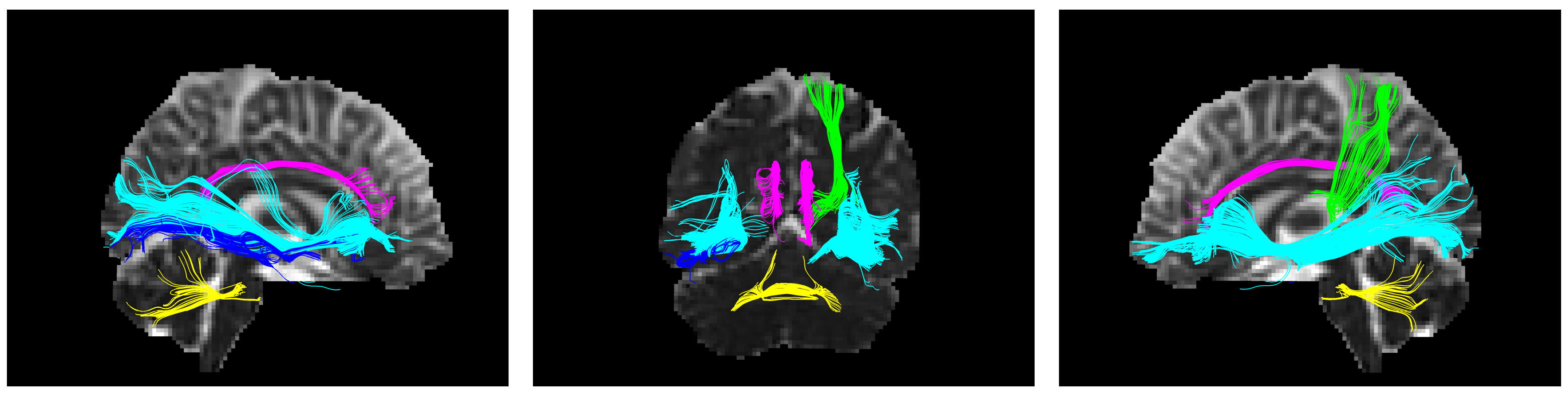

Figure 2 – Eye movements: white matter structures with high in-model frequency in both the JHU and the Juelich-based regression models. Pontine crossing tract (yellow), Cingulum L/R (purple), Posterior corona radiata L (green), fibres passing through the external capsule L/R (cyan), sagittal stratum R (blue).

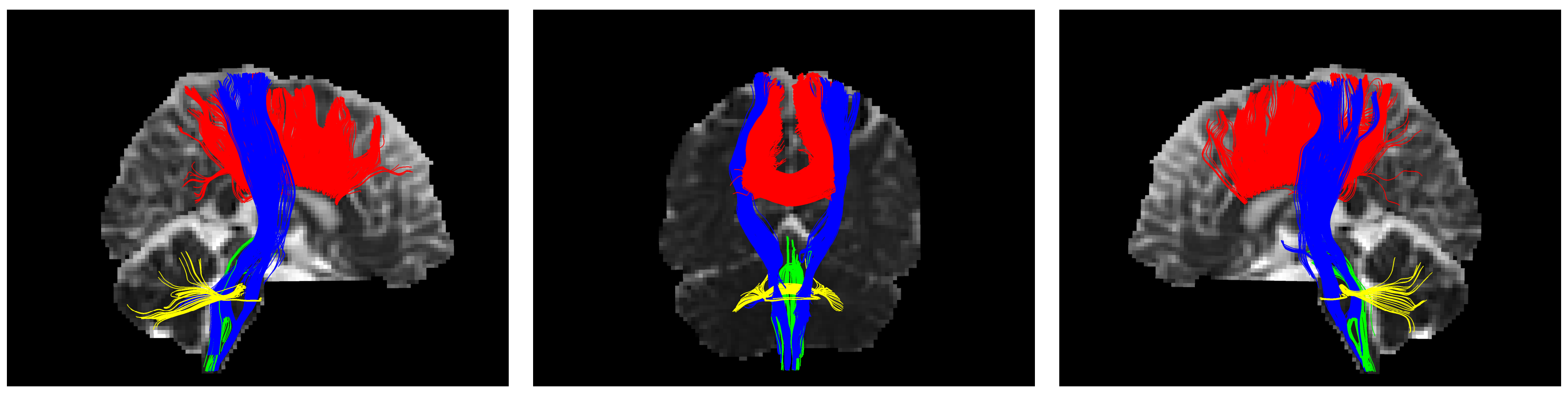

Figure 3 – 'Overlap' between white matter structures showing significant relationships with eye movements and health status at 1 week and 3 months: structures with high in-model frequency in eye movement as well as health status regression models based on the mean FA values for each region. Body of corpus callosum (red; *health: 1 week only*), corticospinal tract L/R (blue; *R: 3 months only*), medial lemniscus L/R (green; *R: 1 week only*), and pontine crossing tract (yellow).

References

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Results

At 3 months post-injury, a group of 8 subjects met the criteria for PCS. The oculomotor parameters distinguishing between this prospective PCS group and the non-PCS patients at 1 week post-injury included measures of reflexive saccades, antisaccades, sequences of memory-guided saccades, predictive saccades, and OSP (Fig. 4b). Regression-models based on the DTI parameters explained 67-95% of the performance variance in these oculomotor measures across the PCS and non-PCS groups (Fig. 4a). Multiple white matter (WM) structures showed frequent associations of FA and/or diffusivity with eye movement performance (Fig. 2, 4c, 4d). Many of these structures also featured frequently in the regression models explaining variance in measures of health status, both at 1 week and 3 months (Fig. 3 & 5). The analyses based on the Juelich atlas also identified several grey matter areas with significant associations between FA and/or diffusivity and both eye movement function and health status (Fig. 6). Amongst the DTI measures, FA was found to have stronger and more frequent associations with oculomotor function and health than measures of diffusivity (i.e., radial or axial diffusivity).

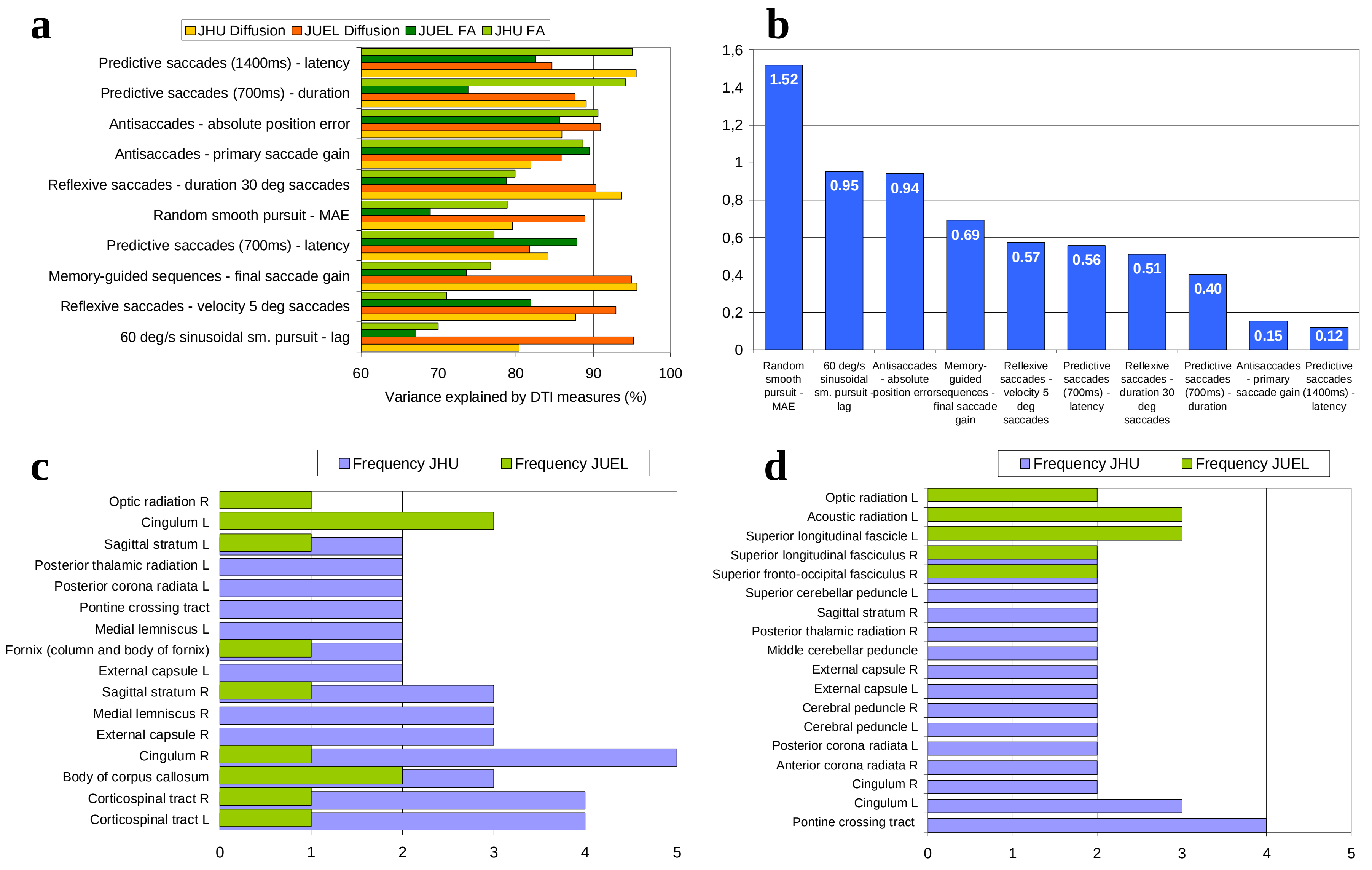

Figure 4 – Eye movements: (a) variance explained by regression-models based on DTI parameters, **(b)** effect sizes for eye movement measures identified in the discriminant function analysis (prospective PCS vs. non-PCS based on eye movement measures at 1 week post-injury), **(c+d)** white matter structures with the most frequent associations with the eye movement parameters listed in figure (b) based on fractional anisotropy (FA) (c) and axial/radial diffusivity (d) (x-axis = in-model frequency in all regression models). Structures as defined by the JHU atlas featured more frequently than Juelich-structures. Structures which were not incorporated more than once in either the JHU or Juelich regression models are not shown.

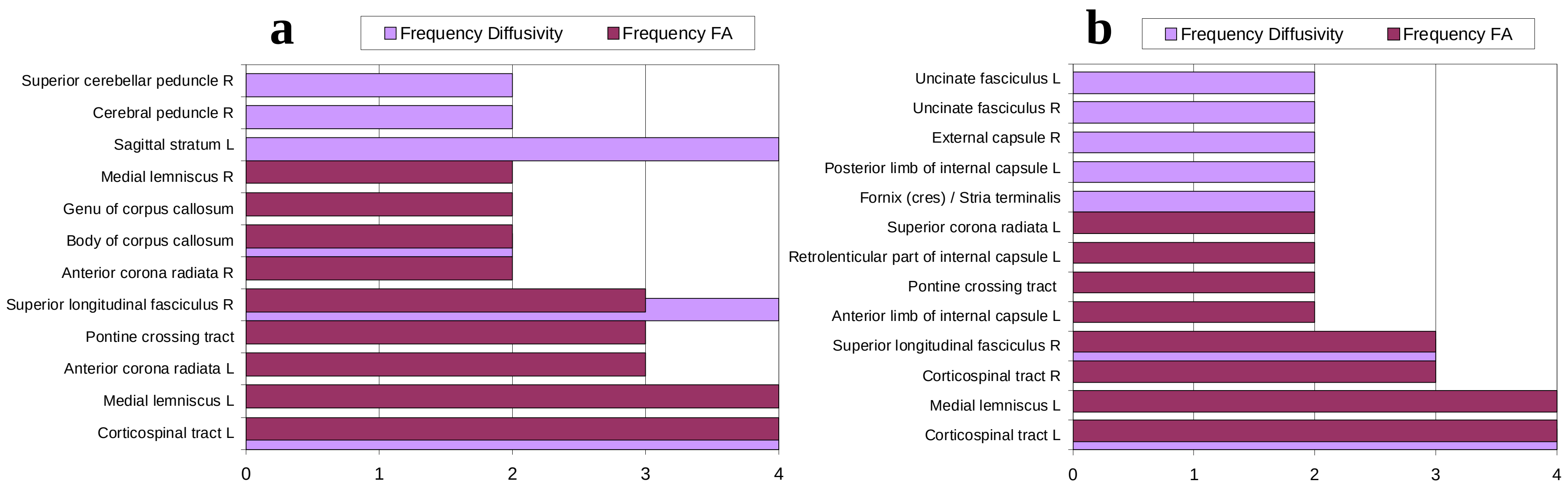

Figure 5 – Health status at 1 week and 3 months: white matter structures (JHU only) with the most frequent associations (high in-model frequency in all regression models, see x-axis) with health status at 1 week **(a)** and 3 months **(b)** based on fractional anisotropy (FA) and/or axial/radial diffusivity. As with the eye movements, structures of the JHU atlas had a higher number of repeated/consistent relationships with health status measures (SF-36 summary measures, Rivermead questionnaires, HADS anxiety score, HADS depression score) than white matter structures of the Juelich atlas.

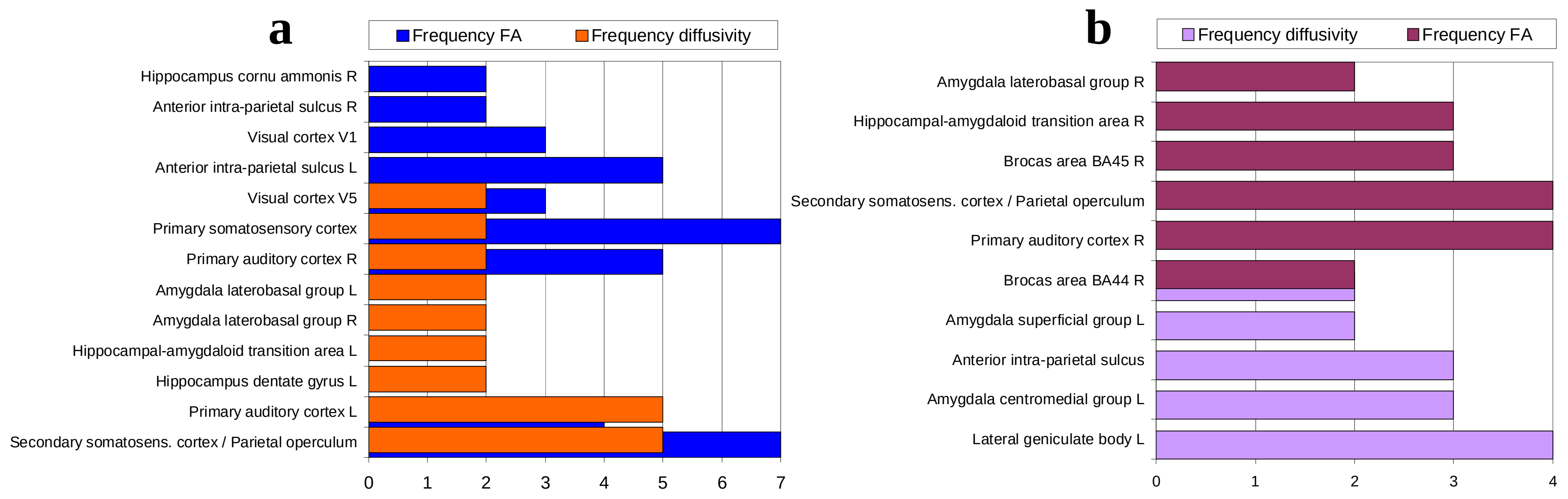

Figure 6 – Eye movements and health status: Juelich atlas grey matter structures with high in-model frequency in the regression analyses for the eye movement parameters **(a)** and measures of health status at 1 week post-injury (SF-36 summary measures, Rivermead questionnaires, HADS anxiety score, HADS depression score) **(b)**.

Conclusions

The results of this study strengthen previous reports of a predictive relationship between early oculomotor impairment and the incidence of poor recovery after mCHI [1,2]. The significant relationship of eye movement disparities between prospective PCS and non-PCS patients at 1 week post-injury with DTI measures of subcortical structural brain integrity (a) corroborates earlier indications of a close relationship between the neuro-biological impact of mCHI and brain function as manifested in eye movement control, and (b) supports previous suggestions [3] that subcortical functionality may be crucial in determining recovery from mild head trauma. These findings and the significant associations between subcortical brain integrity and measures of health status also strengthen previous notions that PCS is not purely a psychological entity but also has an organic substrate.