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Neuroimaging Considerations when Investigating Choroid Plexus Morphology in Idiopathic Psychosis

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The functional implications of the choroid plexus in psychiatric disorders, including the psychosis spectrum have been neglected for many years. However, in 2019 there were 23 articles published in PubMed on this topic in psychiatry with a rapidly increasing trend in the last 10 years. The choroid plexus is an important structure as it is located within the ventricles of the brain, produces cerebrospinal fluid, secretes important neurovascular cytokines, and provides a physical, enzymatic, and immunological barrier to maintain brain homeostasis (Spector et al., 2015). The choroid plexus is uniquely situated in the brain to regulate brain-periphery exchange via choroid plexus epithelial cell tight junctions (blood-cerebrospinal fluid-barrier) and fenestrated brain endothelial cells (De Bock et al., 2014). Peripheral cytokines, stress, and infection have been shown to impact tight junction proteins, which can adversely impact the brain endothelial and/or choroid plexus epithelial cell integrity (Cardia et al., 1995; Coisne and Engelhardt, 2011; Szmydynger-Chodobska et al., 2012). Peripheral cytokines have also been shown to be increased in psychosis (Lizano et al., 2016) and to correlate with molecular signatures in the choroid plexus of patients with schizophrenia (Marques et al., 2009). Therefore, it is possible for peripheral cytokines to adversely impact brain integrity (Lizano et al., 2019; Najjar and Pearlman, 2015). Since neuroimmune alterations are found in psychiatric disorders, in particular psychosis spectrum disorders, researchers have started using neuroimaging to assess neuroanatomical alterations of the choroid plexus (Lizano et al., 2019; Zhou et al., 2020).

Our previously published findings (Lizano et al., 2019) reported choroid plexus volume enlargement (measured via FreeSurfer 6.0) in individuals with mid-course idiopathic psychosis (inclusive of schizophrenia, schizoaffective, and psychotic bipolar disorder)

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Conflict of Interest

The authors do not have any disclosures to report.

compared to both their first-degree relatives and healthy controls. Larger choroid plexus volume in probands was also associated with worse overall cognition, lower gray matter volume, greater ventricular volume, lower structural connectivity and elevated levels of the pro-inflammatory cytokine, IL-6. As this was the first MRI study to investigate choroid plexus volume across the psychosis spectrum, the authors visually rated 24 brain scans as low, medium and high choroid plexus volumes. The raters established high segmentation reliability (ICC = 0.79) and the ratings displayed a moderate correlation with choroid plexus volume (Spearman correlation, $r = 0.44$, $p < 0.01$). In a recent study by (Zhou et al., 2020), the authors investigated choroid plexus morphology (measured via FreeSurfer 5.3) in first-episode schizophrenia (FES) with physiological changes due to long term stress, termed allostatic load, which was created using cardiovascular, metabolic, inflammation, and stress hormone variables. The authors observed choroid plexus enlargements in FES ($n=60$) compared to healthy controls ($n=40$). Higher choroid plexus volume in FES patients was related to greater allostatic load while the lateral ventricles, hippocampus, thalamus and amygdala did not display this relationship with allostatic load. Allostatic load has been implicated with cognitive impairment and psychosis risk (Piotrowski et al., 2019). AL index might contribute to cognitive impairments in FHR-P individuals and patients with psychosis. While the results from this study are promising, the authors did not explicitly state if the choroid plexus segmentation displayed high segmentation reliability (Zhou et al., 2020). As there is a growing interest in the choroid plexus in psychiatry and neurology (Lizano et al., 2019; Tadayon et al., 2020; Zhou et al., 2020), it is critical to develop reliable and accurate tools utilized for choroid plexus segmentation to establish reliable segmentation protocols via visual quality control. This is important since there can be variability in choroid plexus location, voxel intensity differences, and variability in ventricle size, which can impact the proper segmentation of this structure.

Despite the growing evidence supporting choroid plexus implications in psychiatric and neurologic disorders, this region is not a focus of commonly used neuroimaging segmentation pipelines. For example, the FreeSurfer tool uses an atlas generated from manually segmented brain regions from ex vivo MRI scans (Fischl, 2004), which is subsequently used to train a Bayesian model selection algorithm to determine the most probable regions. FMMRIB Software Library (FSL) is a similar tool to FreeSurfer, which uses manually labeled images as its training set with a Bayesian Active Appearance Model that registers and segments each subcortical structure through shape and intensity profiles (Patenaude et al., 2011). The Multiple Automatically Generated Templates (MAGet) pipeline utilizes histological data that are reconstructed and warped to an MRI-based template (Chakravarty et al., 2013). Atlas labels are then nonlinearly registered to a subset of scans to create a set of templates that represents the distribution of age and sex within the sample. Each template is registered to each subject followed by majority vote label fusion. Lastly, 3D Slicer's segmentation pipeline includes both interactive (for manual segmentation) and automated methods and has options for region-based statistical methods, active learning, and expectation-maximization multi-channel segmentation. Semi-automated methods in 3D Slicer have utilized a competitive region-growing segmentation method referred to as GrowCut to segment pituitary adenomas (Egger et al., 2012). The user initializes the image by setting the pixel seeds in the ROI, the seeds will assign labels to

neighboring pixels based on a similarity measure such that the weight of pixels with its neighbor is greater than the current weight, and the process continues until the tracing is stable. Additional post-editing operations include dilation, erosion and island removal.

While these tools provide excellent segmentation in MRI images, they largely focus on the parcellation of cortical or subcortical regions and not the choroid plexus. This results in the choroid plexus being under-measured, not segmented or mislabeled. Future studies in psychosis should be able to utilize atlases that more accurately parcellate the choroid plexus, which may be able to shed new light on pathophysiological mechanisms in psychiatric and neurological disorders.

Currently, the gold standard of choroid plexus segmentation is manual tracing, which can be accomplished with software such as 3D Slicer. However, this process becomes cumbersome when accounting for large-scale multi-site and/or multi-vendor neuroimaging studies. Alternative methods have been developed to overcome this limitation. One alternative method, outlined by (for the Alzheimer's Disease Neuroimaging Initiative et al., 2020), utilizes a Gaussian Mixture Model (GMM) to segment the choroid plexus. The algorithm first uses FreeSurfer masks to isolate the structures within the lateral ventricle, including the ventricular wall, choroid plexus, and CSF. The voxels within this region are then clustered into two groups, one representing the CSF (low-intensity voxels) and another representing the lateral ventricular wall and choroid plexus (high-intensity voxels). Then, the high-intensity clusters are smoothed and further clustered to mask out the highest intensity voxels, which represent just the choroid plexus. Measures between the GMM, FreeSurfer 6.0, and manual segmentations were then compared on brains from healthy controls from the Human Connectome Project (HCP, n=1067) and on a mix of brains from healthy controls, those with mild cognitive impairment, and those with Alzheimer's disease from the Alzheimer's Disease Neuroimaging Initiative (ADNI, n=509) datasets. In both datasets, the GMM outperformed FreeSurfer in parcellating the choroid plexus but had lower accuracy than the manual segmentations.

A second method developed by (Zhao et al., 2020), utilized a deep convolutional neural network (CNN) to parse out the choroid plexus. A standard U-Net model was modified with supplemental parameters to increase segmentation accuracy. Choroid plexus masks from FreeSurfer, overlaid onto preprocessed MRI images, were manually corrected and used as ground truth for training the 3D U-Net. To compare the segmentations between FreeSurfer 6.0 and the 3D U-Net, ten brains from female healthy controls were used as a test sample. The 3D U-Net model demonstrated higher accuracy than FreeSurfer in parcellating the choroid plexus and was more consistent with manual segmentation.

These two methods demonstrate that current techniques in choroid plexus parcellation can and should be improved. While both new approaches are robust, visual inspection and post-processing manual editing is still required. Also, the choroid plexus existing within the 3rd and 4th ventricles as well as within the temporal horns of the lateral ventricles is difficult to segment, even manually, and is usually excluded from automated methods. Furthermore, patients with idiopathic psychosis or Alzheimer's disease have been shown to have larger lateral ventricles relative to healthy controls. Thus, testing automated segmentation models

on brains with larger lateral ventricles is vital for analyzing their efficacy. In addition, creating a choroid plexus atlas for use in commonly utilized segmentation software, such as FreeSurfer, may be helpful in allowing for more precise segmentation to be widely used. By utilizing these new methods for choroid plexus segmentation and improving upon them, new pathophysiological mechanisms related to psychosis may be unearthed.

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