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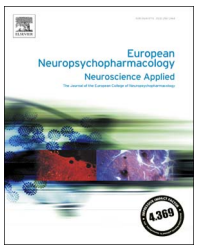

Multi-modal imaging investigation of anterior cingulate cortex cytoarchitecture in neurodevelopment

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Abstract
Multi-modal imaging may improve our understanding of the relationship between cortical morphology and cytoarchitecture. To this end we integrated the analyses of several magnetic resonance imaging (MRI) and spectroscopy (MRS) metrics within the anterior cingulate cortex (ACC). Considering the ACCs role in neurodevelopmental disorders, we also investigated the association between neuropsychiatric symptoms and the various metrics. T1 and diffusion-weighted MRI and ^{1}H-MRS (ACC voxel) data along with phenotypic information were acquired from children (8–12 years) with various neurodevelopmental disorders (n=95) and healthy controls (n=50). From within the MRS voxel mean diffusivity (MD) of the grey matter fraction, intrinsic curvature (IC) of the surface and concentrations of creatine, choline, glutamate, N-acetylaspartate and myo-inositol were extracted. Linear models were used to investigate if the neurochemicals predicted MD and IC or if MD predicted IC. Finally, measures of various

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symptom severities were included to determine the influence of symptoms of neurodevelopmental disorders. All five neurochemicals inversely predicted MD (all $p_{uncorrected}<0.04$, $\beta=0.23$-0.36). There was no association between IC and MD or IC and the neurochemicals (all $p>0.05$). Severity of autism symptoms related positively to MD ($p_{uncorrected}=0.002$, $\beta=0.39$). Our findings support the notion that the neurochemicals relate to cytoarchitecture within the cortex. Additionally, we showed that autism symptoms across participants relate to the ACC cytoarchitecture.

1. Introduction

Neuroimaging studies continuously falter when it comes to the interpretation of morphological measures. The ability to link morphology with the underlying cytoarchitecture and, even more importantly, with cellular functioning could prove paramount to understanding both healthy functioning and deviations from it that lead to behavioral changes and symptoms seen in neurodevelopmental disorders (Bakhshi and Chance, 2015; Casanova and Trippe, 2009; Kotagiri et al., 2014). Here we have applied a multi-modal approach to determine how several metrics, all purportedly related to the cytoarchitecture albeit measured at different scales, relate to each other. It is likely that one biological process (whether it is deviant or not) is reflected not in just one modality, but to varying extents in several modalities. By using a multi-modal approach the strengths of the different modalities complement each other, providing a more complete picture of the topic under investigation (Curiel et al., 2007).

Many morphological measures of the brain can be derived from T1-weighted magnetic resonance imaging (MRI) data. Intrinsic curvature (IC) is a relatively new morphological index of the cortical surface and it has been proposed to relate to the underlying cell density (Ronan et al., 2011). It is posited that expansion of the surface progresses at different rates across the surface dependent on the cytoarchitecture within the cortex. This process of differential expansion results in changes to the surface, measurable as IC. The degree of differential expansion is less in areas of greater cell density due to the accumulative tangential tension applied by the cells hindering expansion (Ronan et al., 2011; Ronan and Fletcher, 2015). This association suggests IC can be used as a quantifiable measure of the cortical cell density.

Mean diffusivity (MD), an index derived from diffusion-weighted MRI data (dMRI), also relates to the cytoarchitecture. Diffusion-weighted MRI is a technique sensitive to the Brownian movement of water molecules within the tissue. MD is the average amount of diffusion by water in any direction within a voxel. Cell bodies and axons form obstacles to water diffusion, thereby reducing MD. MD therefore will vary dependent on cell density (Beaulieu, 2002), where higher cell density will result in lower MD.

Proton MR Spectroscopy (^{1}H-MRS) allows the non-invasive *in-vivo* quantification of several neurochemicals simultaneously within a selected area of the brain. These include neurochemicals that due to their individual cellular localization can also be used as measures of cell density. For instance, the intracellular concentration of glutamate is several thousand times higher than its extracellular concentration (Danbolt, 2001). Since glutamate is a precursor for GABA and for glutamine in glial cells and a constituent of several types of proteins and peptides (glutathione for example) as well as being a the most common neurotransmitter it is assumed that glutamate is present in every cell of the brain (Hassel and Dingledine, 2012). We are therefore confident that glutamate is related to glutamatergic cell density but also to total cell density. N-Acetylasparate (NAA) has been proposed as a marker of neuronal integrity although its concentration varies across neuronal populations limiting its interpretability (Moffett et al., 2007). Myo-inositol (mI) has been proposed as a glial cell marker (Brand et al., 1993). Choline (Cho) has been proposed as a marker of cellular membrane turnover and cell density (Rae, 2014). Finally, Creatine (Cre) is known as a marker of energy usage but is also highly concentrated in neurons and glia rather than extracellularly and may therefore also act as a proxy for cell density.

Several studies to date used multimodal neuroimaging to investigate associations between different imaging measures and symptoms in different neurodevelopmental disorders. For instance, one study used anatomical MRI, dMRI and ^{1}H-MRS to investigate differences between patients with autism spectrum disorder (ASD) and controls (Libero et al., 2015). Differences between groups were found within all measures in several different brain regions. Similarly, a study investigating bipolar disorder found differences in grey matter (GM) volume, white matter (WM) microstructure and functional connectivity in several regions throughout the brain (Johnston et al., 2017). However, neither study integrated the analyses of the different measures nor did they use the same region of interest across the different measures.

The anterior cingulate cortex (ACC), an important region for cognitive control, attention and emotion regulation (Allman et al., 2001), has been widely implicated in various neurodevelopmental disorders, including Tourette syndrome (TS), obsessive-compulsive disorder (OCD), attention-deficit/hyperactivity disorder (ADHD) and ASD. Studies have reported structural (Ecker et al., 2015; Frodl and Skokauskas, 2012; Kühn et al., 2013; Müller-Vahl et al., 2009; Nakao et al., 2011), neurochemical (Brennan et al., 2013; Freed et al., 2016; Naaijen et al., 2015) and functional (Brennan et al., 2015; Hart et al., 2013; Hull et al., 2017; Neuner et al., 2014; Stern et al., 2000) changes, but findings have been inconsistent. TS, OCD, ADHD and ASD may all show increased

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