Perfusion based functional connectivity in autism reveals hypo-perfusion and altered connectivity of the Default Mode Network associated with increased symptom severity

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INTRODUCTION: Blood oxygenation level dependent (BOLD) resting state functional connectivity MRI (rs-fcMRI) is increasingly used to study functional interactions between brain regions in both adults and children with autism spectrum disorder (ASD) and has revealed aberrant patterns of brain connectivity in these populations [1]. More recent studies used Arterial Spin Labeled (ASL) perfusion MRI to assess functional connectivity by quantifying cerebral blood flow (CBF), which is inaccessible to conventional BOLD. This study aims to characterize abnormal patterns of resting state network perfusion in children with ASD using pseudo-continuous ASL (pCASL) in conjunction with autism symptom severity as calculated by the Autism Diagnostic Observation Schedule (ADOS) [2].

METHODS: Twelve right-handed high-functioning children and adolescents with ASD (age [years] mean±SD: 13.0±0.93; 4 unmedicated, 2f/10m) and twelve typically developing (TD) participants (13.8±3.27, 1f/11m) were recruited. Clinical diagnosis of ASD was confirmed with the ADOS, ADI [3], and best clinical judgment. MR data was collected on a 3-T Siemens TIM Trio Scanner (Erlangen, Germany) using a 12-channel head coil. The imaging protocol included a T1-weighted structural MRI and an 8:03 minute resting-state background-suppressed 3D GRASE pCASL [4] (80 L/C-pairs, TR/TE/τ/PLD = 3000ms/22ms/1200ms/1000ms; 26slices; matrix 64x64; voxel 3.44x3.44x5mm). Preprocessing of ASL data included motion correction, CBF quantification with a single compartment model and sinc-subtraction of label and control images [5] (Parameters T1b = 1650, λ=0.9; α=0.8), co-registration to individual T1, normalization to MNI space and smoothing with a Gaussian Kernel (8mm FWHM). Data was restricted to grey-matter voxels and zero-meaned before subjected to a Group ICA using GIFT [6]. ICA model order was determined using the AIC/MDL criterion. The default mode network was identified using GIFT component labeller and visual inspection. DMN_{CBF} was extracted at z-threshold>2 from each participant and correlated with ADOS severity scores, controlling for globalCBF and total intracranial volume (TIV). DMN_{CBF} was also voxel-wise correlated to individual functional connectivity maps (z-maps) computed in the group ICA.

RESULTS: ASD and control participants showed highly similar DMNs (Fig1A). In the ASD group, perfusion in the DMN (DMN_{CBF}) showed a significant negative correlation (r=-0.69 p=0.03) with ADOS severity scores (Fig1B). The DMN_{CBF} showed negative correlations to regional functional connectivity (FC) in areas of the posterior and anterior DMN (Fig2).

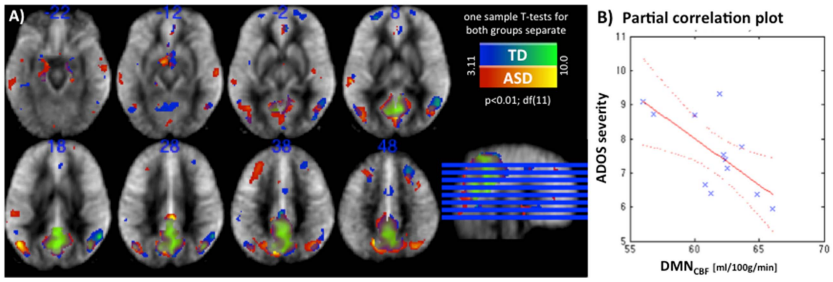

Fig 1 A) CBF based DMN networks for ASD and TD overlaid on mean perfusion maps. **B)** Partial correlation between DMN_{CBF} and ADOS severity score controlled for globalCBF and TIV.

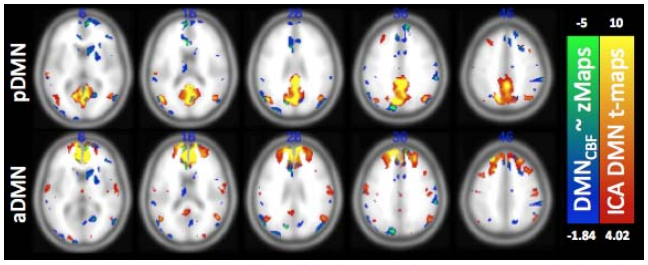

Fig 2 $pDMN_{CBF}$ negatively correlates (blue) to FC values in posterior (top) and anterior (bottom) DMN-subnetwork

DISCUSSION: Our results suggest that altered metabolic activity in the posterior DMN is related to ASD symptom severity. Further, reduced DMN_{CBF} showed altered FC between anterior and posterior DMN suggesting less separability of the DMN subnetworks. Similar findings have been reported in a seed-based functional connectivity analysis, which revealed an association between altered connectivity from PCC to temporal and parahippocampal areas and severity of autism symptoms in individuals with ASD [7]. Moreover, differences in DMN deactivation patterns during a social observation task have been reported for subjects with ASD as well as for those with genetic risk for ASD compared to a non-risk group [8]. Here we demonstrated a relationship between ADOS severity scores and reduced metabolic activity within a brain network that has previously been shown to exhibit altered functional activity and connectivity in individuals with ASD during a socially-relevant task. These findings raise the question of whether there is an association between baseline activity within networks, their functional connectivity and alterations in stimulus processing and/or development of clinical symptoms.

References

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