Characterization of Hemodynamic Alterations in Autism using Resting State fMRI

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Introduction: Autism is a complex neurodevelopmental disorder which lacks a unifying explanation of neuronal pathology at the molecular, cellular, and systemic levels [1]. Systemic approaches using functional magnetic resonance imaging (fMRI) have mainly investigated altered brain activation [2] and connectivity in Autism [3]. These studies attribute all changes in the fMRI signal to underlying neural activity, assuming an unaltered hemodynamic response function (HRF) in Autism. However, recent evidence from molecular/cellular approaches indicate that this may not be true and some neurovascular alterations may exist in the autistic brain [4]. For example, (i) there is evidence that reduced GABA from interneurons in autistic brains [5] may act on micro vessels to increase blood flow (and hence HRF) which may be unrelated to neural excitability [6], (ii) increased expression of nNOS in Autism leads to increased release of nitric oxide, which could elevate the HRF and the fMRI signal in response to the same amount of neural activity [7], (iii) the up-regulation of metabotropic glutamate receptor, mGluR5, found in autistic children, enable the release of vasoactive messengers which could alter the HRF [8], (iv) the global serotonin synthesis is lower in autistic children, but increases gradually to 1.5 times when compared with adult controls [9]. Serotonin is thought to produce a basal constriction of blood vessels [10], therefore, alterations in serotonergic activity could change vessel tone, thus altering the vessel response (and hence HRF) to the vasodilators released by a given amount of neuronal activity [11] and finally, (v) mouse models of Autism have shown increased blood flow with unaltered oxygen extraction [12], which could lead to a large fMRI signal for the same amount of neural activity in individuals with Autism (indicating a larger HRF in Autism). Given this literature, we hypothesized that HRF derived from blind deconvolution of resting state fMRI will be altered in the Autistic brain.

Methods: We obtained fully pre-processed resting state fMRI data from the Autism Brain Imaging Data Exchange (ABIDE), including 392 subjects with Autism and 407 controls. Neither the voxel-specific HRF, nor the latent neural signal is known; rather, only the output of their convolution, i.e. the fMRI signal is measurable. Therefore, deconvolving the resting fMRI signal to recover the underlying voxel specific HRF is an ill-posed problem. Consequently, the deconvolution must be "blind". We used a recently proposed method which considers resting fMRI as a spontaneous pseudo-event-related signal and uses a form of Weiner deconvolution [13]. We obtained three parameters – response height, time-to-peak, and full-width at half-wax (FWHM) – for characterizing the HRF at each voxel in each subject. Two-sample t-tests were performed on the three parameters in order to determine voxel-specific differences of the HRF parameters between the groups.

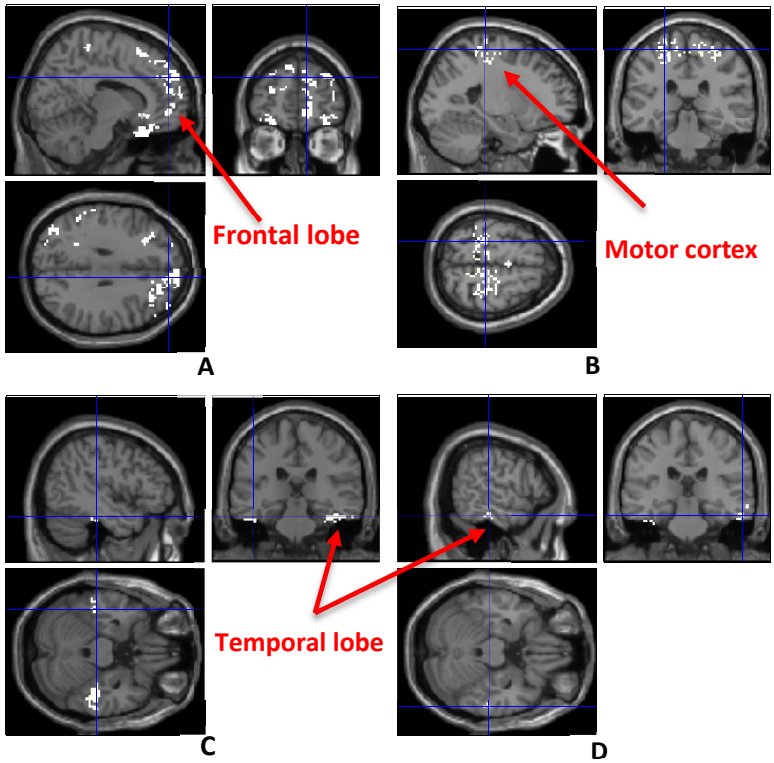

Figure 1. *Spatial maps showing regions with significantly different HRF parameters in Autism as compared to Controls. (A) Response height Autism>Control, (B) Time-to-peak Control>Autism, (C) Time-to-peak Autism>Control, (D) FWHM Autism>Control*

Table 1. *Spatial correlation between HRF parameters (Statistically significant correlations are displayed in bold font.)*

Response Height & Time-to-peak	Time-to-peak & FWHM	FWHM & Response height
-0.0212	**0.5749**	-0.0408

Results and Discussion: Across the entire sample, time-to-peak and FWHM had significant ($p<0.05$ corrected) positive spatial correlation while other HRF parameters were uncorrelated with each other (Table.1). The most significant differences between HRF parameters were present in the frontal lobe, temporal lobe and motor cortex (Fig. 1). Response height was higher in Autism as compared to controls in the frontal lobe (Fig.1A), time-to-peak and FWHM were higher in Autism in the temporal lobe (Fig.1 C and D) and time-to-peak was higher in controls in the motor cortex (Fig.1B). Frontal and temporal lobes are involved in social functions which are compromised in Autism. Accordingly, others have showed decreased activation in these regions in autistic individuals [14]. On the other hand, Autism is characterized by motor hyperactivity and studies have showed increased and atypical connectivity patterns in the motor cortex in autistic individuals [15]. Our results indicate that regional variation of neurovascular coupling should be thoroughly investigated in Autism before fMRI-based findings of altered activity and connectivity are directly attributed to underlying neural activity.

References: [1] Geschwind, *Cell*, 135, 391–395, 2008. [2] Eilam-Stock et al, *Brain*, 137(1): 153-171, 2014. [3] Deshpande et al, *Front. Hum. Neurosci*, 7, 2013. [4] Reynell et al, *Dev Cogn Neurosci*, 6, 72–79, 2013. [5] Fatemi et al, *J Autism Dev Disord*, 40, 743–750, 2010. [6] Kocharyn et al, *J. Cereb. Blood Flow Metab.* 28, 221–231, 2008. [7] Attwell et al, Nature,468, 232–243, 2010. [8] Fatemi et al, *Anat Rec (Hoboken)*, 294, 1635–1645, 2010. [9] Chugani et al, Neurology, 45:287–295, 1999. [10] Cohen et al, *Prog. Neurobiol*, 50,335–362, 1997. [11] Blanco et al, *Am. J. Physiol. Heart Circ.Physiol*, 294, H2855–H2863, 2008. [12] Weiss et al, *Neuropharmacology,* 63, 837–841, 2012. [13] Wu et al, *Med Image Anal* 17:365–374, 2013. [14] Ciaramidaro et al, *Schizophr Bull.*, 2014 (in press). [15] Nebel et al, *Front Syst Neurosci*. 8: 80, 2014.