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Project Report

Gradients of cortical hierarchy in Autism

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Abstract

Autism is a developmental condition associated with altered functional connectivity. We propose to re-frame the functional connectivity alterations in terms of gradients that capture the functional hierarchy of cortical processing from sensory to default-mode network regions. We hypothesized that this hierarchy will be altered in ASD. To test that, we compared the scale of gradients in people with autism and healthy controls. The present results do not support our hypothesis. There are two alternative implications: either the processing hierarchies are preserved in autism or the scale of the gradients does not capture them. In the future we will attempt to settle which alternative is more likely.

Keywords

gradients, autism, functional connectivity, resting-state fMRI, ABIDE, cortical hierarchy

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Introduction & Aims

Autism Spectrum Disorder (ASD) is characterised by local and global disruptions of functional connectivity (FC) (Vissers et al. 2012). These disruptions are accompanied by a range of cognitive-behavioural symptoms, such as atypical socio-emotional or language processing. Several theories attempt to explain the nature of FC alterations and their impact on brain function: reduced long-distance (global) and increased short-distance (local) FC (Belmonte 2004), the 'underconnectivity hypothesis' (Just 2004) and reduced central coherence (Happé 2013). While these theories can explain local/regional anomalies in specific ASD subgroups, they do not generalize across the ASD spectrum. We propose to address these limitations with a different perspective on brain organization, based on the concept of connectivity gradients.

Connectivity gradients (Margulies et al. 2016) provide a low-dimensional approximation of whole-brain connectivity. Each gradient can be represented as a whole-brain spatial map that describes relationships between brain systems. Margulies et al. (2016) derived the gradients from healthy participants and found that the first ('principal') gradient is anchored in sensory regions on one side and transmodal regions on the other, including the default-mode network (DMN). This organization captures the major hierarchy of processing in the cortex, from sensory inputs to their abstract representations. We hypothesized that ASD might alter this hierarchy and the alteration would be reflected in the gradients. There are two ways the gradients could be affected: by changes of their scale or by the shifts of specific brain regions within the gradients. Here we explore the former option.

Hence, we set out to recreate the gradients from the orginal paper by Margulies et al. (2016) in a publically available and pre-processed autism imaging dataset (http://preprocessed-connectomes-project.org/abide/). We investigate potential differences in the scale of the gradient, its overlap with the DMN and its overlap with maps corresponding to the associated hierarchical cognitive processing as reported in figure 4 of Margulies et al. (2016).

Approach

To make the project practically feasible in the course of Brainhack, we used pre-processed male adult data (age range: 18-55) from the ABIDE dataset (Martino et al. 2013, http://preprocessed-connectomes-project.org/abide/). We chose to use the most fine-grained parcellation available (Craddock 400) that was pre-processed with the C-PAC pipeline and did not include global signal regression but did include bandpass filtering (Craddock et al. 2011). The processing pipelines for all analyses described here can be found on the Autism Research Centre github repository and, with more guidance, on the GitHub front end. In short, we selected only subjects without missing time-series to avoid dimension mismatches in the correlation matrix. We thus included 160 subjects: 91 with autism (age: 24.55±5.25) and 69 controls (26.15±7.69), matched for age ($p = 0.14$). We then ran diffusion embedding (Coifman and Lafon 2006) on the thresholded (>10%) matrices and ba

ckprojected the diffusion components for each individual subject using the pySTATIS package. We then saved the individual-level gradients in nifti format. We also created nifti maps of every 10th percentile of the primary gradient.

Our primary outcome measure was the scale of the gradient as estimated by the linear fit to the sorted gradient values. Individual fits were visually inspected to quantitatively assess the fit; examples can be found on the above mentioned GitHub website. As a secondary measure we computed a goodness of fit ratio for the gradient values inside and outside of brain masks obtained from NeuroSynth that accompanied the keywords listed in figure 4 of Margulies et al. 2016. For the binned principal gradient we also calculated the average z-score inside these masks in unthresholded meta-analysis maps from neurosynth for the same keywords.

Results

Gradient slopes show no distinguishable difference between the autism and neurotypical groups (Fig. 1), although the variability of the principal gradient seems somewhat larger in the autism group. The goodness of fit for the principal was compared against mask derived from thresholded NeuroSynth keywords as listed in Fig. 2. Both the autism as well as the neurotypical group show the highest goodness of fit with the default-mode network (DMN) as would be expected from Margulies et al. 2016. The overall order of the goodness of fit for the two groups did not differ. Analysis of the 10 percentile bins of the principal gradient also showed little divergence between the two groups (Fig. 3).

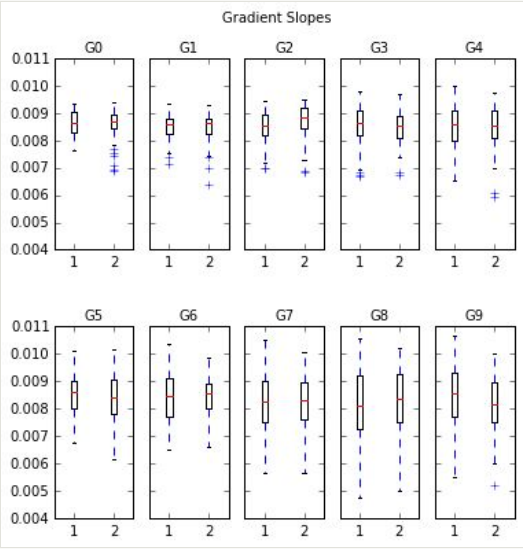

Figure 1.

Linear fit of gradient slopes for the top 10 gradients for each group (1 == neurotypical individuals; 2 == individuals with autism).

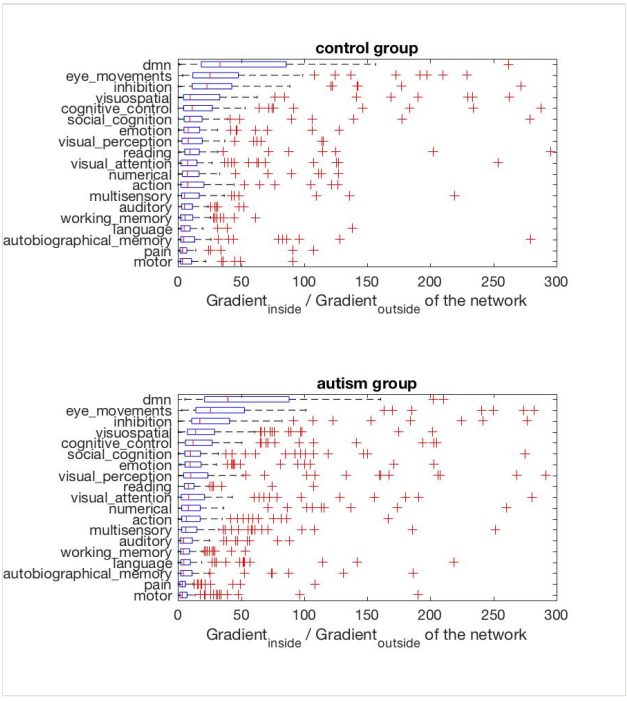

Figure 2.

Goodness of fit for principal gradient. Ranked according to the median goodness of fit for both groups.

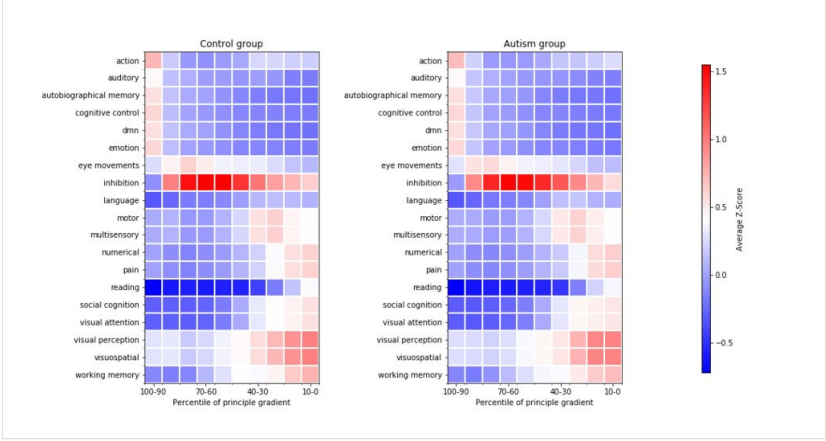

Figure 3.

Average z-scores obtained from unthresholded reverse-inference neurosynth meta-analysis activation maps. We divided the principle gradient into percentiles and used this to create a mask. We then calculated the average z-score inside this mask on neurosynth maps.

Limitations and future directions

In order to improve feasibility, the present study used one specific pre-processed parcellation template. This greatly improved processing time at the cost of reduced spatial specificity. The orginal paper by Margulies et al. (2016) used a voxel-based approach; it is very well possible that the parcellated resolution in the present study might not be high enough for an accurate goodness-of-fit measure. Future implementation of this pipeline will look into un-parcellated data. In addition, it is our intention to validate the current results against other parcellations of the same dataset. Furthermore, we will seek to explore other properties of the principal gradient and run more rigorous statistical tests. Finally, we will explore the second option for alterations of the gradients: shifts in the location of specific brain areas within the gradient space.

Autism is well known for its heterogeneity and it is possible that, by averaging over the entire cohort, potential subtle sub-group effects are lost. Future analysis will look into combining topographical gradient information with phenotypic information provided with ABIDE.

Acknowledgements

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