Multivariate analysis of atypical patterns of fMRI connectivity modulation in ASD

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INTRODUCTION

Mapping patterns in the brain to patterns in behaviour is not straightforward and relationships may or may not map on to pre-defined ontologies on either side. **Canonical correlation analysis** (CCA) can explore uncharted linear multivariate relationships between sets of variables [1,2]. Within an ASD cohort, we have applied this technique in **five tasks** seperately on fMRI brain data depicting atypical connectivity modulation and related it to corresponding behavioural measures. This allows characterising cognitive systems probed by fMRI tasks simultaneously in terms of brain properties and behavioural characteristics for a given cohort.

DATA

Data from the **EU-AIMS longitudinal european autism project.** ASD participants completed resting-state fMRI and a scan during one or more of the following five fMRI tasks: Hariri, Flanker, Social reward, Monetary reward, Theory of mind [3].

Seven behavioural measures were selected from a larger array on the basis of their probing of ASD dysfunction along the major affected domains (social, repetitiveness, sensory) as well as possible **ADHD comorbidity** and IQ [4]. Missing behavioural measures were imputed using random forest regression.

METHOD

Preparation

In each task, we prepared the brain data for inferences about atypical connectivity modulation by using a three step procedure.

1. Estimate **functional connectivity** (FC) matrices per individual.
2. Model **task potency** (task FC modulation away from the resting state FC baseline) [5].
3. Build a **normative model** relative to typically developing controls to assess the atypicality of task potency in each edge [6].

For the brain data we now construct a **subjects by edges** matrix of atypicality scores. For the behavioural data we similarly contruct a **subjects by clinical variable** matrix from the same subjects. We will relate these to one another using CCA.

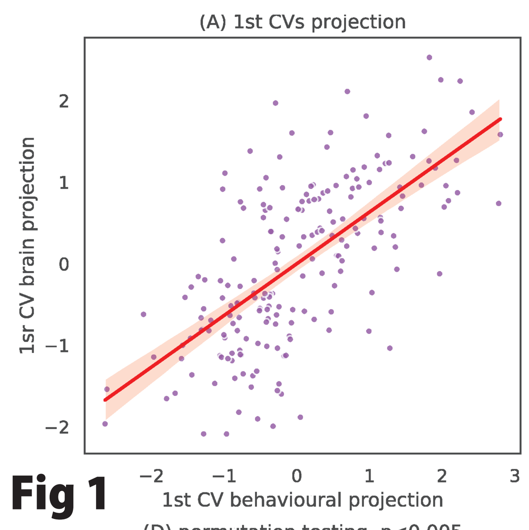

Fig 1

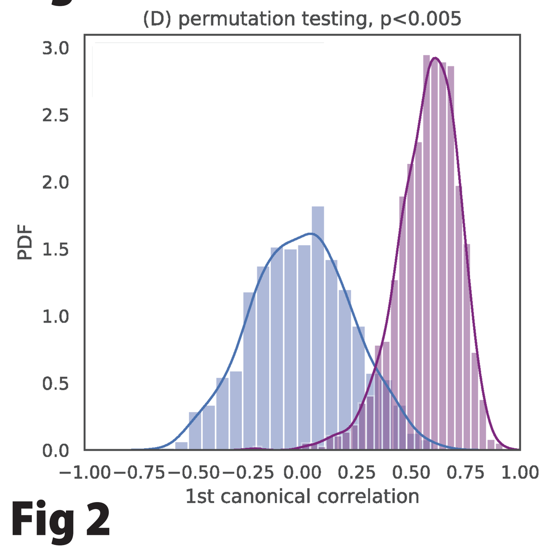

Fig 2

Canonical Correlation Analysis

CCA simultaneously finds linear combinations of sets of variables such that they maximally correlate. Here, the data projection onto the first of these **'canonical variates'** describes the main mode of co-variation that exists between behavioural variation and brain variation for our data matrices - as an example in one of the tasks [Fig 1].

In order to assess the **stability** and **generalizability** of the relationship found in each task, we utilize bootstrapping with 10-fold cross validation and assess similarity of CCA weights across folds - as well as generating test (purple) and null (blue) distributions of correlation values to assess significance [Fig 2].

RESULTS

First canonical relationship nonspurious in each task ($p<0.05$). CCA weights highly stable across folds (generally cross-fold correlations > 0.99).

Fig 3a: Top 10% **brain** regions with the highest absolute loadings from the CCA-analysis as summed over edges, in the different tasks.

Fig 3b: Loadings for **behaviour** variables from the CCA-analysis in the different tasks. Loadings follow a generally similar pattern across tasks indicating ASD severity.

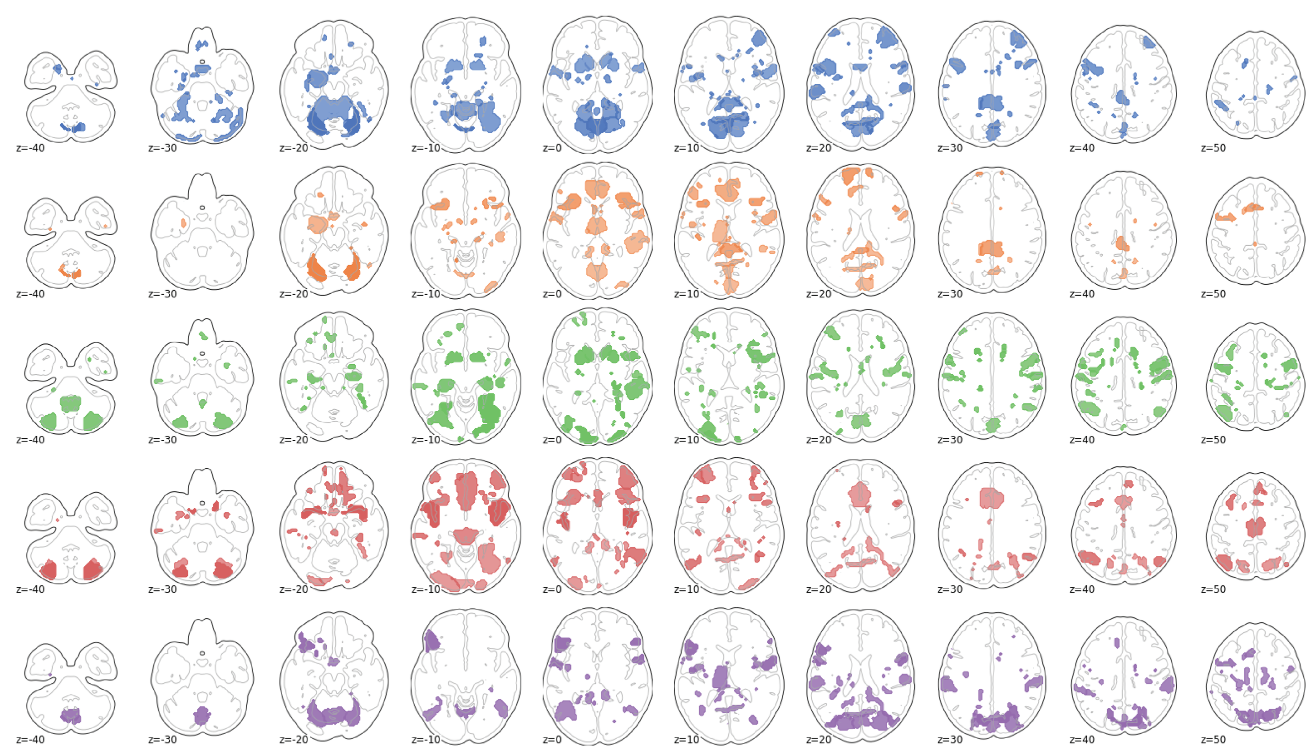

Fig 3a

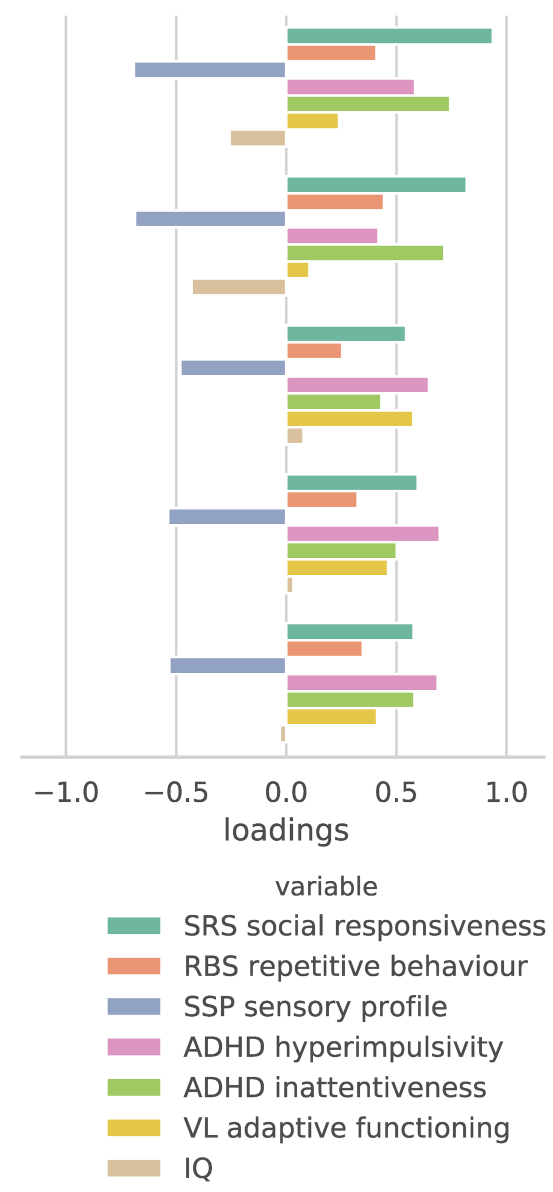

Fig 3b

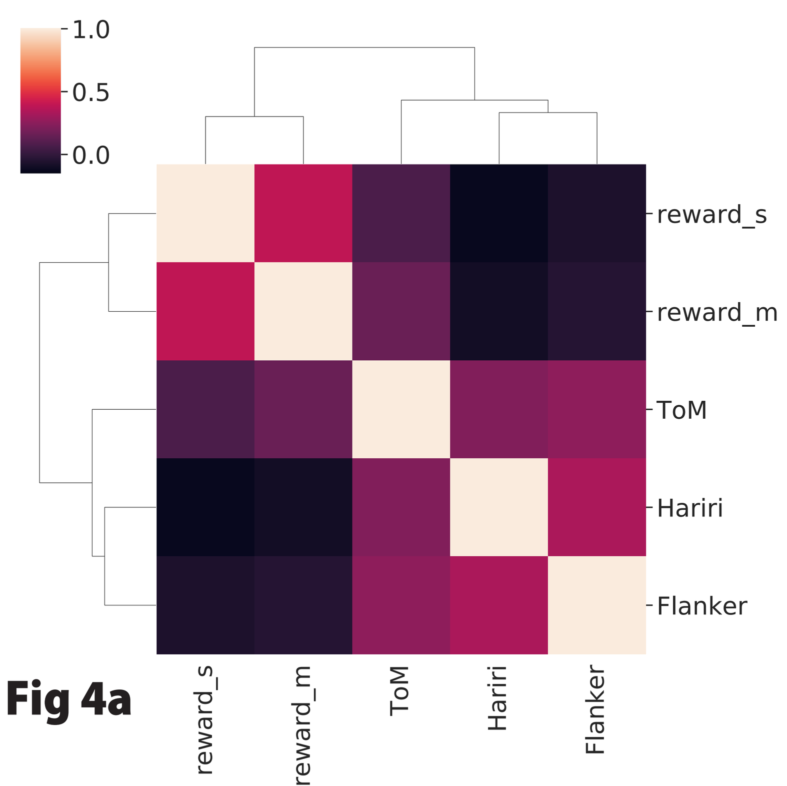

Fig 4a

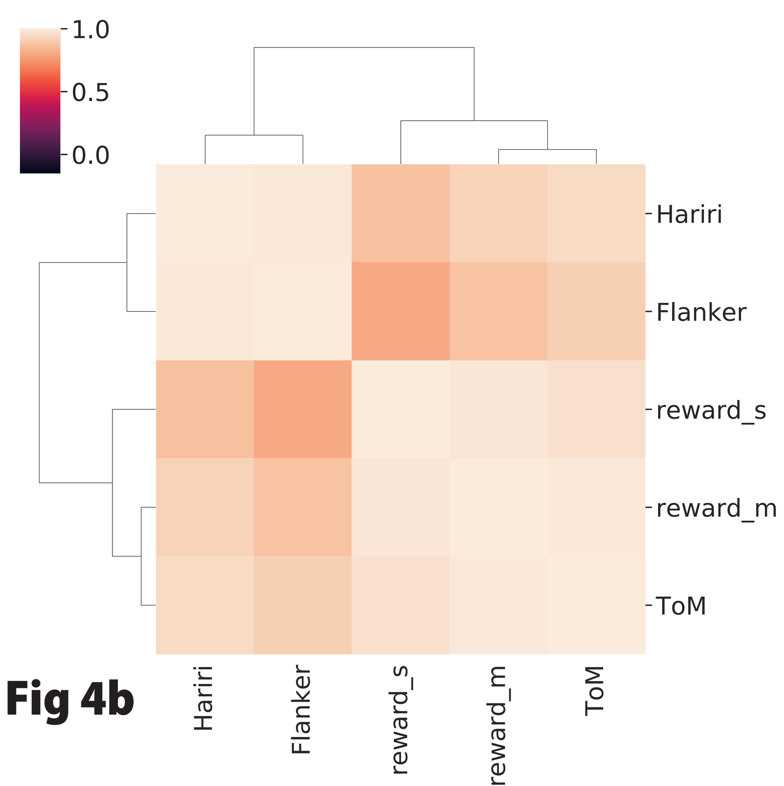

Fig 4b

Fig 4a: **Clustering** heatmap of cross-task correlations for CCA brain loadings. Correlations high between the two reward tasks and between Hariri/Flanker. Theory of mind occupies a middle ground between the clusters.

Fig 4b: Clustering heatmap of cross-task correlations for CCA behavioural loadings. High correlations between all tasks, and clustering into two main groups in a similar vein to the brain clustering, with the exception that ToM is now clustered with the reward tasks instead of Hariri/Flanker.

CONCLUSIONS

❋ The behavioural patterns associated with atypical connectivity modulation are similar across tasks - but broadly separate into two classes.

❋ Brain patterns associated with clinical variables are generally far less similar, but still contain the same two clusters.

❋ We can use CCA as a feature detection tool to explore the brain/behaviour relationship that underlies the cognitive construct probed by an fMRI task - and how these relate across tasks.

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