DOPAMINE ALTERS THE SENSORIMOTOR-ASSOCIATIVE FUNCTIONAL GRADIENT IN PARKINSON'S DISEASE

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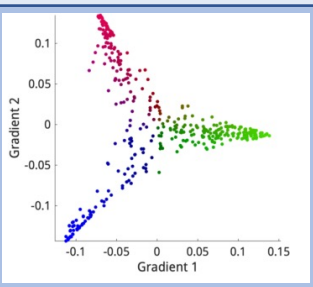
ABSTRACT

Parkinson's disease is primarily characterised by altered dopaminergic neuromodulation. Dopamine therapy remains the mainstay treatment in Parkinson's disease. Exploring how dopamine modulates the functional organisation of networks may help to uncover novel mechanisms that contribute to cognitive and motor performance in Parkinson's disease. We find significant changes in functional gradient scores of the dorsal attention, ventral attention and default mode networks between patients ON and OFF dopamine treatment.

BACKGROUND

- Parkinson's disease is primarily characterised by altered dopaminergic neuromodulation.
- Whilst structural and functional connectivity changes have been documented in individuals with Parkinson's disease (1,2), novel techniques can offer further insight into how changes in neuromodulatory function affect the hierarchical organisation of the brain (3).
- A hierarchical organisation of brain function that spans from unimodal (sensorimotor) to heteromodal (associative) regions has been replicated in the healthy brain across populations (4), however the influence of dopaminergic modulation on this gradient remains unexplored.



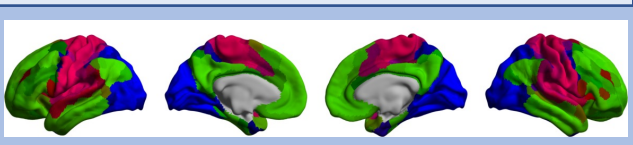


Figure 1. Margulies principal gradient: cortical organisation that spans unimodal (sensorimotor) to heteromodal (associative) regions (4).

AIMS

We apply the framework of functional cortical gradients to investigate the influence of dopamine on brain organisation in Parkinson's disease.

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METHODS

- Resting state fMRI
  - 27 individuals with Parkinson's disease
    - ON dopamine therapy and;
    - OFF dopamine therapy
  - 19 healthy age matched controls
- We performed standard fMRI preprocessing and extracted cortical gradients using the BrainSpace toolbox (6)

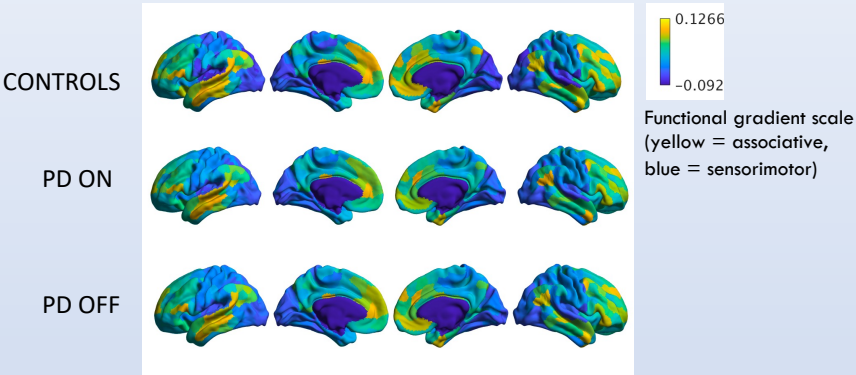

Figure 2. Mean second gradients mapped to cortical surfaces

- We identified regional expression profiles for genes of catecholaminergic receptors (Allen Brain Atlas microarray dataset (7)) and measured differences in receptor density between regions along the gradient axis.
- We related expression density to gradient scores at each region of interest.
- Spatial permutation testing and principal component regression was done (8,9,10).

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RESULTS

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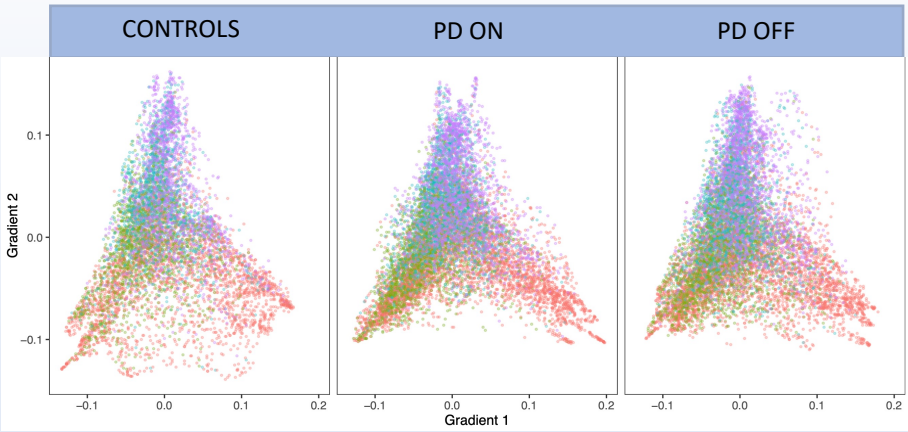

Figure 3. Relationship between the first and second (principal) gradients scores for all participants by group.

Colour key: network hierarchy of functional organisation: Red = visual and somatomotor networks, Green = ventral attention and dorsal attention networks, Blue = limbic and frontoparietal control networks, Purple = default network.

We found compression of the second gradient (sensorimotor-associative) in Parkinson's disease participants compared to healthy controls ($p < 0.001$).

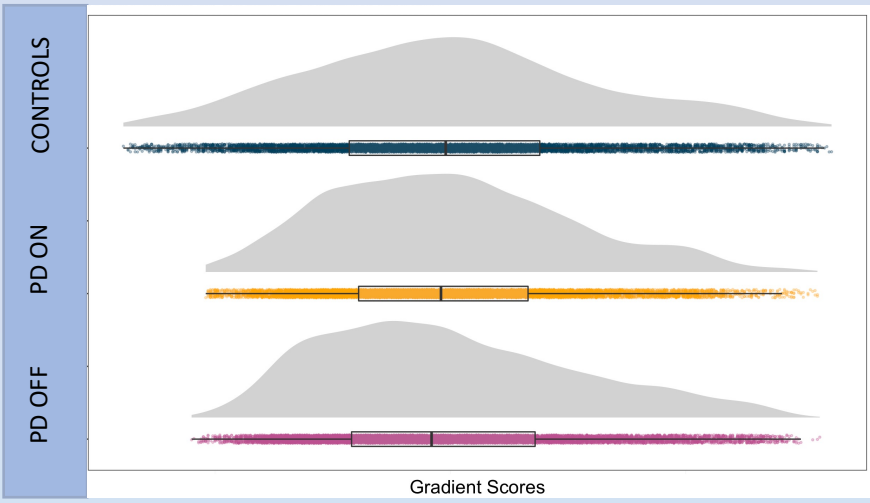

Figure 4. Distribution of principal gradient scores

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RESULTS

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At the network level (n=7), significant differences in gradient scores between the Parkinson's disease participants ON vs OFF dopamine were found in the dorsal attention, ventral attention and default mode networks ($p < 0.001$).

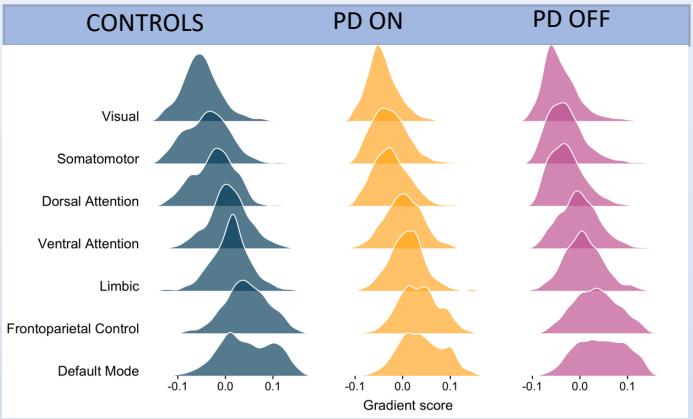

Figure 5. Distribution of principal gradient scores by network.

Preliminary results reveal no significant correlations between differences in gradient scores and dopamine receptor expression density (DRD1 and DRD2).

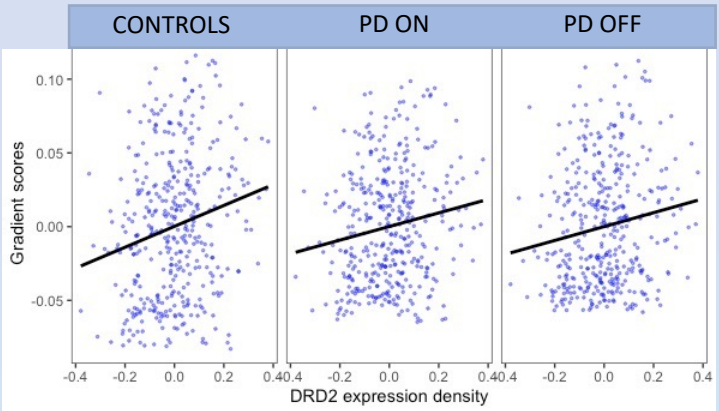

Figure 6. Relationship of mean principal gradient score and DRD2 gene expression density per node (n=400).

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CONCLUSION

- Together, our results demonstrate that the principal hierarchical organisation of unimodal-to-heteromodal function is altered (compressed) in Parkinson's disease.
- The compression seen in the Parkinson's hierarchical organisation suggests reduced segregation between sensory and association regions, driven by compression of the sensorimotor systems.
- Changes at the network level were observed between patients ON vs OFF dopamine treatment.
- These preliminary findings suggest a novel mechanism by which dopamine may act on cognitive and motor function in Parkinson's disease through network differentiation.

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