Sex Moderates the Relationship between Functional Connectivity and Remission in Late-life Depression

Andrew R. Gerlach[1], James D. Wilson[1], Helmet T. Karim[1,2], Howard J. Aizenstein[1,2], Carmen Andreescu[1]

1. Psychiatry, University of Pittsburgh; 2. Bioengineering, University of Pittsburgh

Introduction

- Major depressive disorder accounts for more disability-adjusted life years than any other mental illness[1]. Late-life depression (LLD) presents with greater heterogeneity and risk of associated cerebrovascular disease and cognitive decline[2].
- Despite a pressing need for effective treatment, first line antidepressants are only ~30% effective at achieving remission[3], and up to a third of patients remain treatment resistant over subsequent antidepressant trials[4]. Hence identifying biomarkers of treatment response is crucial for improving outcomes.
- Early changes in resting state functional connectivity (rsFC) are one promising modality for measuring network-based neurobiological predictors of treatment response.
- Despite established sex differences in prevalence[5] and clinical profiles[6] of depression and evidence for sex differences in rsFC[7], no studies have examined the rsFC sex differences in depression.
- **AIM**: Investigate sex differences in rsFC predictors of LLD treatment response

Methods

- **Design and Participants:** We analyzed data from two renewals (Circuits2 and NEMO) of one study (NIMH MH076079) with 51 and 30 participants that underwent resting state fMRI before and 1 day after commencing standard antidepressant treatment. Remission was defined as Montgomery-Asberg Depression Rating Scale (MADRS) ≤10 after 12 weeks.
- **Functional Connectivity:** The Shen50 parcellation[8] (excluding cerebellum) was used to calculate an 82x82 FC matrix by correlating the average time series between regions at baseline and day 1. Differential connectivity (DC) was calculated by subtracting baseline FC from day 1 FC. FC measures were harmonized across study and scanner type using ComBat[9] while preserving variance related to age, sex, race, education, cumulative medical burden, and baseline depression severity.
- **Statistical Analysis:** DC differences between remitters and non-remitters were assessed with independent *t*-tests for males and females separately. Region-wise difference measures were calculated by averaging all positive and negative edges for a region that were significant at the 0.05 level (uncorrected).

$$t_i = \frac{1}{N-1}\sum_{j\neq i}^{N} t_{ij} I(p_{ij} < 0.05) \text{ for region } i$$

- **Prediction Models:** Seven random forest models containing different combinations of demographic, clinical, baseline edge-wise FC, and edge-wise DC predictors were generated with remission status as the outcome (Table 1). Predictive AUC was used to assess model fit with 30 repetitions of a 90/10 training/test split; within-fold Monte Carlo cross validation was performed with 100 training sets uniformly sampled between 50% and 80% (Figures 2 and 3). Gini importance was used to assess variable importance (Figure 4).

Results

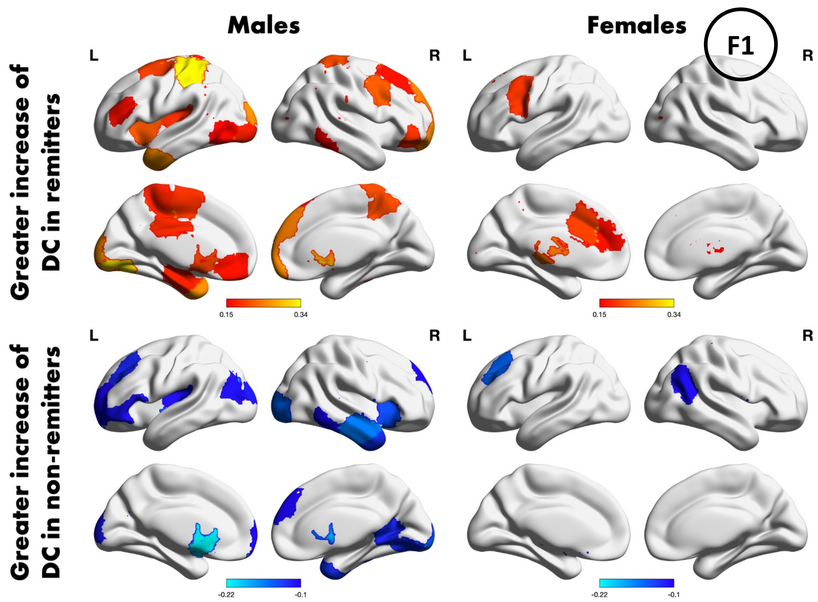


Figure 1. Region-wise average *t*-statistic for the positive and negative differential connectivity (DC) differences between the remitter and non-remitter groups by biological sex. Overall, males showed greater differences between groups, particularly increased FC in the left postcentral gyrus and decreased FC in the left caudate. Increased FC in the right thalamus and decreased FC left dorsal lateral prefrontal cortex differentiated remitters and non-remitters among females.

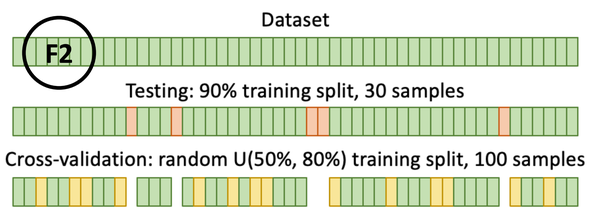
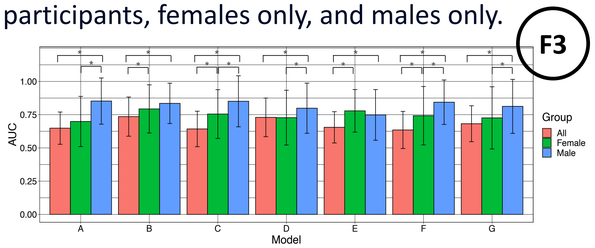


Figure 2. Predictive model strategy. Random forests models were evaluated for predictive AUC on thirty 90/10% training/test splits with nested Monte Carlo cross validation (100 folds).

Variables	Model						
	A	B	C	D	E	F	G
Demographic/clinical	x	x	x	x	x	x	x
Baseline depression severity	x			x		x	x
Baseline connectivity		x		x	x		x
Differential connectivity			x		x	x	x

Table 1. Variables included in the 7 fitted models.

Figure 3. Model G performance with all participants, females only, and males only.



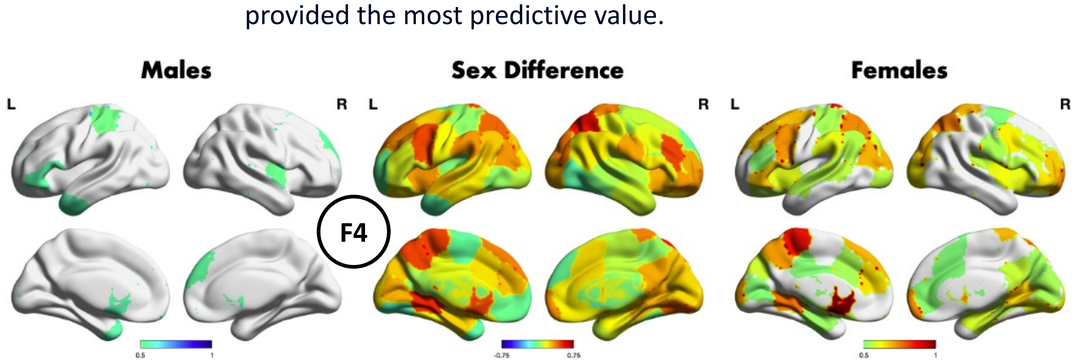


Figure 4. Region-wise average variable importance for predicting remission status in Model G (Table 1) for males (left) and females (right). Sex differences (female minus males) are shown in the center panel. The left caudate and nucleus accumbens led importance values for both males and females. Other important regions for females were focused in the left paracentral lobule, left lingual gyrus, and bilateral parietal lobes. For males, left temporal pole, left inferior frontal gyrus, right dorsolateral prefrontal cortex, and right caudate provided the most predictive value.

Discussion

- Changes in functional connectivity one day after commencing antidepressant treatment differentiating remitters from nonremitters show marked differences between males and females (Figure 1).
- Sex differences are not adequately captured by sampling including sex as a covariate in the predictive model.
  - The predictive AUC of the random forest models consistently improved after splitting males and females into separate models, regardless of the variables used to fit the model.
  - Only the connectivity of the left caudate/nucleus accumbens was an important predictor in both males and females.
- Clinical applications of precision psychiatry may require a more careful consideration of the role of sex than is currently typical.

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