

FUNCTIONAL BRAIN CONNECTIVITY IN OLDER WOMEN WITH URGENCY URINARY INCONTINENCE

Hypothesis / aims of study

We evaluated functional connectivity of brain regions involved in bladder control *post hoc* and compared differences between continent and urgency incontinent women, and explored changes caused by positive response to pelvic floor muscle therapy.

Study design, materials and methods

54 women over age 60 years with urgency urinary incontinence (UUI), and 10 continent women, had fMRI scans during full-bladder urinary urgency provocation, before and after (in UUI) therapy. Therapy 'responders' had >50% reduction in leaks on 3-day bladder diary. *A priori* selected regions of interest (ROIs) were: right insula, medial prefrontal cortex (mPFC), and dorsal anterior cingulate cortex/supplementary motor area (dACC/SMA). Generalized psycho-physiological interaction (gPPI) was used to calculate 'effective connectivity' between ROIs during urgency at low and high bladder volume conducted using our urge provocation task using small bolus infusion and withdrawal of fluid [1]. We conducted a one-way ANOVA pre-treatment on groups (continent vs responders vs non-responders) and a two-way mixed ANOVA (responders vs non-responders and pre- vs post-therapy) using false discovery rate (FDR) correction. Principal component analysis was used to assess origins of connections within our chosen 18mm radius spherical ROIs. Exploratory voxel-wise connectivity analyses were conducted between each ROI and the rest of the brain to assess other brain regions which interact in the continence mechanism, beyond those chosen from the working model.

Results

ROI-ROI connectivity yielded no significant results with multiple comparisons correction, but trends (grey charts in fig 1) showed connectivity differences between dACC-Insula and mPFC-dACC based on group (responders vs non-responders) and between dACC-Insula at baseline (controls vs UUI). Principal component analysis showed that the chosen ROI fully encompassed the densest cluster of origin of connections (spherical ROIs in fig 1).

Baseline exploratory voxel-wise analyses showed connections to the primary visual, motor/sensory and midcingulate. In responders, connectivity values changed towards that of the controls after therapy, whereas in non-responders, consistent changes were not seen (white violin plots, fig 1).

Interpretation of results

Principal component analysis: The examination of spatial distribution of connections within the original ROIs suggests that these were appropriately selected, if slightly off centre, prioritizing the dACC, anterior insula, and anterior mPFC. In future analysis, we will adjust our ROI centre to encompass these connectivity clusters.

gPPI analysis: No ROI comparisons survived correction for multiple comparisons. However, we do comment on trends: In the low volume task, insula-mPFC connectivity changes differently in responders to therapy (away from 'normal') compared to non-responders (towards 'normal'). Such differences may suggest a compensatory reaction in responders.

At high volume, changes are slightly larger and tend more towards 'normal' in responders rather than non-responders (fig 2).

Exploratory voxel-wise analysis: the occipital areas play a significant part, particularly the lingual area (visualization and analysis of the logical order of events). These areas form connections with the insula and dACC and may be part of the coping mechanism for urgency, since responders tend to 'normalize' these connections post-therapy. Non-responders stay in the 'normal' range which may suggest why these strategies are not useful – their connections are not 'abnormal' initially. The connection between the dACC and visual cortex is present even at low volumes, though it diminishes after therapy, possibly indicating a change in perception of the test (pre-urgency), if indeed this represents a visualization mechanism.

The mPFC exhibits differential connections with the precuneus, cingulum and post-central gyrus, as expected from our working model. Our previous work showed these areas, but this analysis shows direct connectivity between the areas, dependent on continence status, suggesting that this connection might be involved in the therapeutic mechanism.

The insula exhibits differential connections to the motor/sensory cortex, which may support our original hypothesis concerning the SMA-Insula connectivity, but might suggest a revision of (or addition to) our ROI coordinates.

The caudate (motor processing, process learning, inhibitory control of actions), putamen (movement regulation) and thalamus (motor/sensory relay, sleep regulation, consciousness), have differential connections to the dACC at rest, suggesting motor processing mechanisms which may be differently dependent on continence status and altered through.

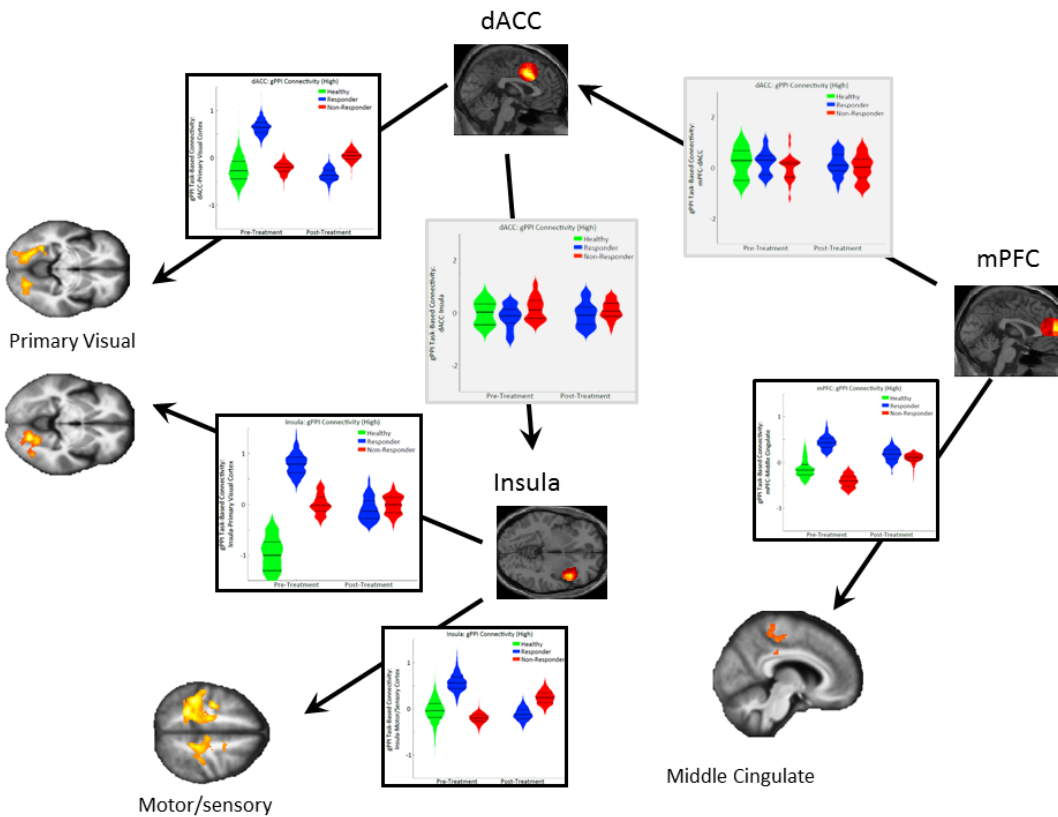


Figure 1, interconnectivity of brain areas during urgency. 'Principal component' origins of connections shown for mPFC, dACC and Insula. Grey plots do not survive corrections for multiple comparisons. Violin plots show distribution of connectivity parameters within the cluster (mirrored vertically) with 25, 50 and 75th centile marks shown.

Concluding message

This builds upon work identifying brain areas involved in UII by showing how regions interact, how interaction differ between disease states and how interaction changes with therapy. Overarching themes can be observed. Principal component analysis has shown that our selected ROIs are appropriate but suggest a slight positional shift. Figure 1 serves to show that identified connections in responders, tend towards the 'normal' level after therapy (though they may overshoot). In contrast, non-responders have connections which more often move away from normal, or do not change. This theme provides some supportive evidence that our decision to stratify by response may show two subsets of UII: (1) predominantly caused by a breakdown in brain control of the continence mechanism and which is represented in those who respond to a behavioural therapy which targets cerebral control, and hence 'normalizes' connectivity; and (2) may have another, yet unknown, cause, represented by those who do not respond well to therapy and do not show consistent 'normalization' of connectivity. This suggestion, (initially demonstrated by baseline differences in brain activation of responders and non-responders [2]) has also been supported by our structural studies (in press). If confirmed by future study, identification of UII subsets could help therapy trials and targeting of specific UII types, as well as advance understanding of the brain bladder mechanism.

References

1. Clarkson BD, Tyagi S, Griffiths DJ, Resnick NM. Test-retest repeatability of patterns of brain activation provoked by bladder filling. *Neurourol Urodyn.* 2016. DOI:10.1002/nau.23153
2. Griffiths D, Clarkson B, Tadic SD, Resnick NM. Brain Mechanisms Underlying Urge Incontinence and its Response to Pelvic Floor Muscle Training. *Journal of Urology.* 2015;194(3):708-715

Disclosures

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