MAPPING EFFECTIVE CONNECTIVITY IN THE MOUSE BRAIN USING GRANGER CAUSALITY

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Target audience. Researchers and clinicians interested in resting state fMRI connectivity and its aberrations in brain disorders.

Introduction. Resting-state BOLD functional magnetic resonance imaging (rsfMRI) has been widely employed to investigate the functional organization of the human brain and infer functional connectivity between different brain regions [1]. The use of rsfMRI to describe brain connectivity typically rests on the use of symmetric measurements of correlation that are intrinsically insensitive to the direction of information flow. Recent attempts to implement directional measures of rsfMRI connectivity in the human brain have been described using computational methods such as Granger causality [2]. The application of these methods to describe the topology of the human default network (DMN) has highlighted consistent features, including an established role of the posterior cingulate cortex as informational "sink" [3-4]. By using tight control of physiological and motion artefacts, we have recently demonstrated that the mouse brain contains distributed rsfMRI networks including a putative "default-mode"-like network (DMN) [5,6]. Research on the topology and evolutionary role of this distributed neural system in genetic mouse models can crucially advance our understanding of the elusive pathophysiological contribution of DMN connectional aberrations recently described for multiple neurodegenerative and psychiatric disorders [7]. In an attempt to map the direction of information flow within this network and relate this to the organization of the human DMN, here we have applied Granger Causality (GC) to describe the dominant direction of causation among four key nodes of the mouse DMN, namely the prefrontal and posterior cingulate cortex, and temporal parahippocampal association areas.

Methods. All experiments were carried out in accordance with Italian regulations governing animal welfare and protection. rsfMRI experiments were performed on male 20-24 week old C57BL/6J (B6) mice (n=41) as previously described [5,6]. Briefly, mice were anaesthetized, intubated and artificially ventilated; blood gases and arterial pressure were monitored continuously. rsfMRI timeseries were acquired under halothane anaesthesia (0.7%). **Image acquisition**: All experiments were performed using a 7.0 Tesla MRI scanner, using a single-shot EPI sequence with TR/TE 1200/15 ms, flip angle 30°, matrix 100 × 100, field of view 2 × 2 cm^2, 24 coronal slices, slice thickness 0.50 mm, 300 volumes and a total rsfMRI acquisition time of 6 min. **Image preprocessing**: rsfMRI timeseries preprocessing included motion correction, spatial normalization to an in-house mouse brain template, spatial smoothing (Gaussian kernel, FWHM of 0.6 mm), regression of motion traces and the mean ventricular signal, and band-pass filtering ($0.01 < f < 0.08$ Hz). **Granger causality analysis:** We defined multiple sets of seed ROIs within the mouse DMN that can be related to analogous key subsystems of the human DMN: (1) prefrontal cortex, (2) posterior cingulate/retrosplenial cortex, (3) left and (4) right temporal parahippocampal association cortices. For each set of ROIs we computed pairwise Granger Causality [2], pairwise-conditional Granger Causality [2] along with dominant directional causality [8] defined as the difference between causality in each direction.

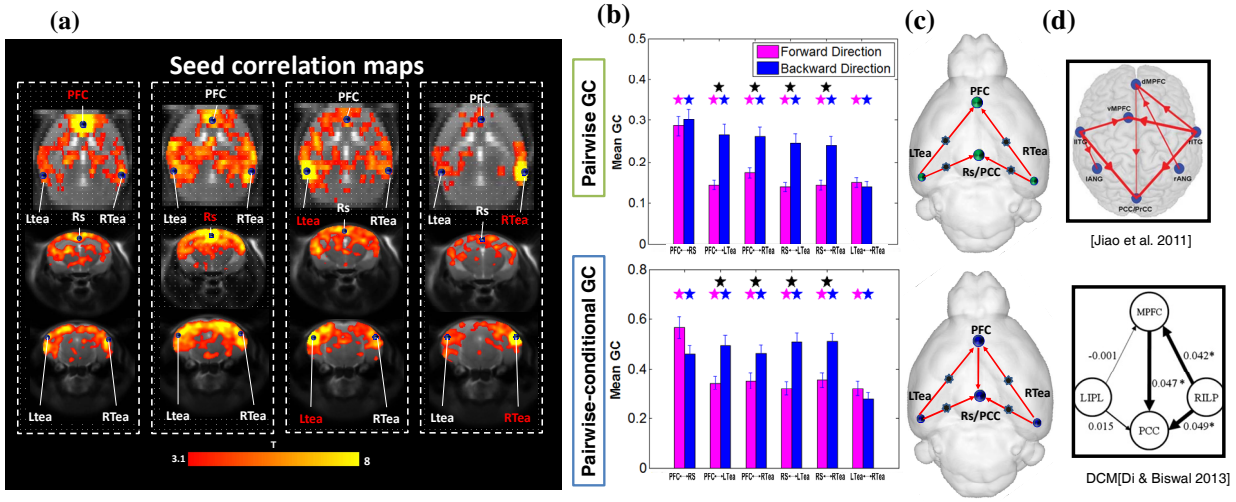

***Figure 1**: **(a)** Correlation maps for each of the selected DMN seeds (indicated in red). **(b)** Mean forward and backward Granger causality for each pair of seed regions. Black star indicates the presence of a statistically significant dominant direction ($p < 0.05$, t-test). **(c)** Schematic of connections exhibiting a dominant direction overlaid on a three-dimensional representation of the mouse brain ($p<0.05$, t-test). The connection between PFC and Rs did not reach statistical significance although a trend was evident for many ROI sets. **(d)** Directional connectivity by pairwaise or conditional GC for the human DMN are shown or comparisons. For **(b)**,**(c)** & **(d)** top: Pairwise GC, bottom: Pairwise-conditional GC.[PFC: prefrontal cortex; PCC/Rs: posterior cingulate/retrosplenial cortex; LTea/RTea: left/right temporal parahippocampal association cortices].*

Results and discussion. Results from a representative set of ROIs are reported in Figure 1. Consistent with previous findings [6], seed-based mapping highlighted the presence of reciprocal connections between the selected ROIs within a distributed network of areas that define the mouse DMN homologue. Pairwise Granger Causality revealed the presence of dominant directional information flow between key regions of this network. Specifically, dominant postero-anterior information transfer was observed between parahippocampal regions and prefrontal cortex. Importantly, a "sink"-effect of the posterior cingulate was also observed. Conditional Granger Causality produced largely consistent results, with evidence of directional information flow along the same pathways highlighted with the pairwise Granger Causality. Importantly, analogous directional connectivity patterns have been described in the human DMN by using both Granger Causality [3] and dynamic causal modelling [4].

Conclusion. Our data demonstrate the feasibility of inferring direct connectivity patterns from rsfMRI recordings in the laboratory mouse and support the empirical notion that an evolutionary precursor of the DMN circuit may be present also in lower mammal species like the laboratory mouse.

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