Intrinsic directional connectivity in large-scale functional networks of the mouse brain

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Background: Resting-state fMRI (rsfMRI) has been extensively used to describe the intrinsic functional connectivity of the brain. However, classic rsfMRI mapping relies on correlational measurements insensitive to the direction of information flow among regions. Computational approaches enabling a description of directional functional connectivity have been recently proposed, providing a novel interpretative dimension to rsfMRI-based connectivity and its aberrations. However, anatomical or neurophysiological validations of the statistical inferences employed to describe directional connectivity in rsfMRI are lacking.

By taking advantage of the known anatomical connectivity of the mouse brain, here we validated a computational framework based on Granger Causality (GC), a measure of directed causation, to infer directional connectivity in large-scale rsfMRI mouse network characterized by mono-directional and reciprocal axonal connectivity, including the mouse default-mode network (DMN).

Methods: C57BL/6J mice (n=41) were imaged under controlled sedation using a single-shot EPI sequence (TR/TE 1200/15 ms) at 7 Tesla as in Sforazzini et al., 2014. Images were motion corrected, spatially normalized, band-pass filtered, smoothed and regression of motion traces and the mean ventricular signal was applied, followed by haemodynamic deconvolution (Wu et al., 2013). Group and subject-level analyses GC were computed using single node conditioning in a set of regions-of-interest encompassing the ventro-hippocampal-prefrontal network as unidirectional “ground truth” axonal system, and the mouse salience and DMN as reciprocally-connected systems.

Results: GC was able to successfully resolve hippocampal-prefrontal dominant functional connectivity in the mouse brain along mono-directional projecting ventro-hippocampal neurons both at single subject and population level (p<0.01). Converging directional connectivity patterns (p<0.01) from lateral association cortices towards midline prefrontal cortical areas were identified in large-scale heteromodal mouse rsfMRI systems such the salience and DMN. Interestingly, we found directional connectivity within the DMN to be reversed in a mouse model of autism.

Conclusions: We demonstrate that GC-based methods can be optimized to reliably infer directional information flow in rsfMRI networks characterized by mono-directional and reciprocal anatomical connectivity. The robust directional signatures identified suggest that large-scale spontaneous cortical activity in the resting mammalian contain dominant intrinsic directional paths that hierarchically guide information flow between heteromodal cortical centers.