Mapping the Human Default Arousal Network Connectome

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Introduction: A robust understanding of networks that modulate arousal (which together with awareness comprises consciousness) is critical for studying mechanisms of unconsciousness such as brain injury [1,2], anesthesia [3], and sleep [4]. However, little is known about the network properties of human subcortical arousal regions. This gap in knowledge stems largely from the inability of standard neuroimaging methods to delineate subcortical arousal nodes and map the complex subcortical white matter architecture making up arousal networks. In this study, we combine ultra-high-resolution *ex vivo* High Angular Resolution Diffusion MRI (HARDI) [5-6] with corresponding histopathology to map the local connectivity properties of neurotransmitter-specific arousal nodes. Based on this methodology, we propose a neuroanatomic terminology for the human Default Arousal Network (DAN) to guide future investigations on arousal systems.

Methods: Four brain specimens from individuals who died of non-neurological causes were analyzed in this study. In specimen 1, the hemispheres and cerebellum were dissected to isolate the brainstem, thalamus, hypothalamus, and basal forebrain. The isolated tissue underwent a HARDI sequence in a 4.7 Tesla small-bore scanner (b=4000 s/mm^2, 60 diffusion-encoding directions, 600μm spatial resolution). Specimens 2-4 were scanned in a 3 Tesla Siemens TimTrio scanner (b=4000 s/mm^2, 90 diffusion-encoding directions, 750μm spatial resolution). Specimen 1 was serially sectioned, and DAN nodes were traced with guidance from corresponding histology (hematoxylin and eosin/Luxol fast blue) and immunohistochemistry (tyrosine hydroxylase and tryptophan hydroxylase). DAN candidates are the brainstem arousal nodes (Locus Coeruleus (LC), Pedunculotegmental Nucleus (PTg), Ventral Tegmental Area (VTA), Dorsal/Medial Raphe (DR/MnR), Laterodorsal Tegmental Nucleus (LDTg), Periaqueductal Grey (PAG), Parabrachial Complex (PBC), mesencephalic reticular formation (mRt) and Pontis Oralis (PnO)), hypothalamic nodes (Lateral Hypothalamic Area (LHA), Tuberomammillary/Supramammillary Nucleus (TMN/SUM)), Basal Forebrain nodes (Nucleus Basalis of Meynert/Substantia Innominata (BNM-SI), Nucleus of the Diagonal Band (NDB)), and Thalamic nodes (Reticular Nucleus (Ret), Paraventricular Nucleus (PaV), Intralaminar Nucleus (IL)). DAN nodes were similarly traced with respect to selected HE-LFB and TH/TPH sections in specimens 2 and 3, and tracing was performed with a neuroanatomic atlas [7] in specimen 4. HARDI data from all four specimens was processed for both deterministic and probabilistic tractography with FSL [8].

Results: Deterministic tractography in each specimen revealed significant and widespread projection connectivity in DAN nodes (brainstem nodes to thalamic/hypothalamic/basal forebrain nodes) and association connectivity (brainstem nodes to ipsilateral brainstem nodes) across most nodes, particularly for glutamatergic (PBC) and cholinergic (PTg) centers (Figure 1A). Commissural connectivity (brainstem node to ites contralateral node) revealed a more selective connectivity pattern, mainly crossing the midline via the posterior commissure (PCOMM), with the majority of connections associated with the PBC, PTg and PAG (Figure 1B). A probabilistic

DAN connectivity matrix (with a connectivity probability metric as described in (3)) was generated (Figure 2), which revealed a similar specimen-averaged connectivity profile as seen with deterministic fiber tracking.

Conclusion: Our tractography results reveal a highly heterogenous connectivity profile within the DAN. In particular, there are multiple hub regions (nodes that are diffusely connected to the rest of the DAN nodes) found in the probabilistic connectivity matrix, with Ret serving as the most highly connected hub, which is directly supported by prior electrophysiologic data in animals [9,10]. Novel projection and association-specific hubs, including PnO and LDTg are also observed, indicating a need to further study and classify the network properties of these nodes in humans.

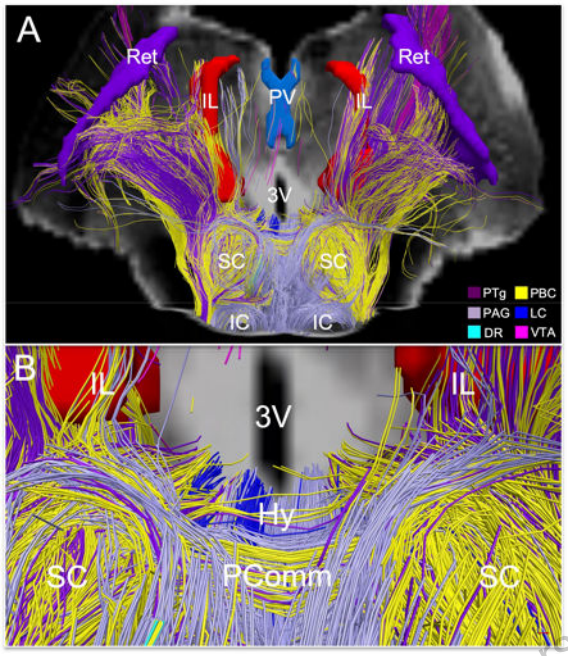

Figure 2: Dorsal view of deterministic fiber tracts emanating from extra-reticular arousal nodes **(A)** and a zoomed dorsal view on commissural pathways **(B)**.

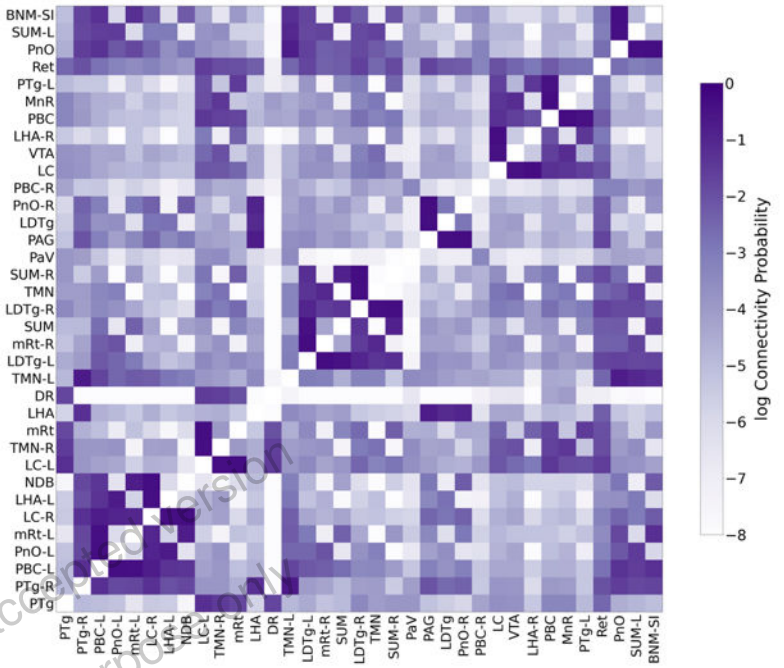

Figure 1: A map of connectivity probability determined from probabilistic tractography on DAN nodes (averaged between specimens 2-4).

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