# Posterior Medial Corticothalamic Connectivity and Consciousness

In a foundational study published in this issue of *Annals of Neurology*, Fernández-Espejo et al[1] report that diagnostic categories of disorders of consciousness can be stratified by diffusion tensor imaging (DTI) of connections among specific components of the default-mode network (DMN).[2] The DMN includes the corticocortical and thalamocortical connections of the medial prefrontal, posterior medial regions (including the posterior cingulate [PCC] and precuneus [PCu]) and the temporoparietal junction (TPJ), which are identified by functional neuroimaging techniques to demonstrate strong functional connectivity.[2,3] The DMN contains some of the most metabolically active regions of the human brain at rest[4] and is proposed to play a key role in maintaining a state of readiness of internal representations accessed during self-monitoring or shaping of motivated actions.[5] Prior studies have linked outcomes of vegetative state (VS) and minimally conscious state (MCS) after brain injuries to the strength of correlation of blood oxygen level-dependent signals across the DMN.[6]

In the present study,[1] the authors employ DTI and probabilistic tractography methods to evaluate the structural integrity of the white matter in 19 VS patients, 27 MCS patients, and 6 patients emerged from MCS, using measurements of mean fractional anisotropy (FA; a quantitative measure of directionality reflecting restriction of movement of water molecules). FA values of white matter connections between the thalamus and PCC/PCu, and PCC/PCu and TPJ components of the DMN demonstrated a specific correlation across the diagnostic categories; notably, this statistical linkage of the PCC/PCu-thalamic and PCC/PCu-TPJ FA values to outcomes appeared against a background of global reductions in white matter connectivity measured across all patients that did not differ across the groups.

Several prior observations in patients with disorders of consciousness can be related to these findings. As seen in the modeled thalamocortical tracts measured in the study, many of the inferred fiber trajectories pass through the posterior aspects of the corpus callosum. This region is particularly vulnerable in the setting of traumatic injuries[7] as a result of mechanical shearing,[8] and has been identified in prior studies as an important indicator of enduring disorders of consciousness.[9] The observations also directly support the previous suggestion that vegetative state may reflect a functional disconnection syndrome involving the posterior medial cortical regions.[10] The specific correlation of PCC/PCu and thalamic connectivity with VS and MCS may relate to the known role of focal injuries in the central thalamus in producing VS and MCS in some patients,[11] and further supports a proposed common pathophysiologic basis of disorders of consciousness in the altered function of posterior medial corticothalamic connectivity.[12]

Anatomical connections of the thalamus and PCC/PCu include a dominant projection from the anterior thalamic nucleus to the PCC, but also important projections from the anterior intralaminar nuclei (central lateral, paracentral, and abutting paralaminar neuronal populations); the latter group of nuclei broadly innervate the entire posterior medial complex, including adjacent regions of the medial parietal cortex and retrosplenial cortex.[13] Focal bilateral injuries to this collection of central thalamic nuclei can produce longstanding disorders of consciousness.[11] Moreover, following diffuse traumatic brain injuries a selective and graded loss of neurons across the thalamic intralaminar nuclei is correlated with outcomes, with the earliest involvement evident in the anterior intralaminar components.[14] Thus, the correlation of PCC/Cu-thalamic connectivity with outcomes in the present study likely also indexes the degree of central thalamic deafferentation following injury.

Fernández-Espejo et al[1] further report that the integrity of corticothalamic connections with PCC/PCu statistically separate the group of MCS patients who demonstrate only nonreflexive behaviors (such as auditory localization or visual tracking) and those MCS patients able to follow commands or exhibit more complex behaviors. This important finding provides the first evidence of a structural substrate difference associated with these clinical features of patients across the MCS spectrum (described as MCS/− or MCS/+, respectively[15]). This difference associates a greater degree of thalamic deafferentation with lower level behavioral profiles and suggests that MCS/− patients may also have broader deficits of thalamocortical activation. Although patients in the study showed no significant difference in structural connectivity of the thalamus with the medial prefrontal node of DMN compared to controls, the loss of thalamic-PCC/PCu connections likely also marks a

 

major alteration in thalamic functional connectivity with the frontal cortices (which may arise via specific mesocircuit mechanisms[16]).

Support for such a joint role of PCC/PCu and central thalamus in determining the level of overall cerebral synaptic activity and the state of consciousness in the setting of broad functional deafferentation comes from a recent human anesthesia study in normal subjects. Xie et al[17] found that both the thalamus and precuneus showed selective significant decreases in regional blood flow during anesthetic coma compared with a wakeful baseline.[17] Most importantly, however, increased blood flow in thalamus and PCC/PCu selectively correlated with brief recovery of consciousness with administration of physostigmine, an acetylcholinesterase inhibitor, while subjects were in an otherwise stable plane of anesthesia.

In the aggregate, the Fernández-Espejo et al[1] study indicates that the structural integrity of connections between the thalamus and PCC/PCu may index outcomes following severe brain injuries and possibly provide a substrate for developing interventions.[12] The founding editor of *Annals of Neurology*, Fred Plum, often made the remark that "consciousness is a post-rolandic process"; these measurements support the view that posterior medial corticothalamic connectivity plays an essential role in the state of wakeful consciousness.

## Potential Conflicts of Interest

Nothing to report.

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DOI: 10.1002/ana.23671