◆ Human Brain Mapping 00:00–00 (2017) ◆

Functional Neuroimaging After Severe Anoxic Brain Injury in Children May Reveal Preserved, Yet Covert, Cognitive Function

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Abstract: A growing body of evidence has confirmed that, after severe brain injury in adults, motoric and task-dependent factors that are essential for reliable communication, frequently interfere with an accurate assessment of cognitive status. In the current study, resting state functional magnetic resonance imaging (fMRI) in children who have sustained an anoxic brain injury following a near drowning incident suggests a similar pattern; preserved cognition amidst severe motoric impairment that effectively precludes accurate clinical diagnosis at the bedside. *Hum Brain Mapp 00:000–000, 2017.*

Key words: consciousness; vegetative state; minimally conscious state; fMRI

COMMENTARY

While the last 20 years have produced a veritable explosion of imaging-based methods for the assessment of structural and functional changes following severe brain injury in adults (e.g., Fernández-Espejo et al., 2015; Naci et al., 2014; Owen et al., 2006), the corresponding literature in children remains relatively sparse. A leading cause of serious brain damage in children is non-fatal drowning, with the highest rates occurring among those 1–4 years of age. Outcomes vary from complete recovery to brain death, depending upon the extent of neurological damage. Between these two extremes, lie the so-called "disorders of consciousness" (DOC), including minimally conscious state, vegetative state, and prolonged coma. Assessing residual brain function in adult DOC patients is notoriously difficult because impairments in motoric responses often mask the true extent of preserved cognitive functioning, a situation that is likely to be exacerbated in pediatric populations (Owen, 2017).

In this issue, Ishaque and colleagues publish the third in a remarkable and challenging series of studies that have employed voxel-based morphometry (Ishaque et al., 2016), diffusion tensor imaging (Ishaque et al., 2017) and now resting state fMRI (this issue) to study the extent and effects of nonfatal drowning on the brains of a group of 11 children whose injuries occurred in the first few years of life. Until recently, the prevailing view in this area was that the neuropathologic consequences of near-drowning predominantly affected gray matter, rather than white matter, largely based on what is known about the metabolic demand profiles of those tissue types and the higher concentrations of excitatory neurotransmitter receptors in gray matter. In 2016, Ishaque and colleagues first challenged this notion using voxel-based morphometry and showed that, in child survivors, damage occurs in both gray and white matter in a pattern that relates to the vascular territory of deep perforating vessels (predominantly the lenticulostriate arteries). Because gray matter loss was localized to the basal ganglia nuclei, thalamus, cerebellum, and sensorimotor cortex, while white matter loss was also largely localized to areas of the motor system, one important implication of this finding is that, like adult DOC patients (Owen et al., 2006), the true cognitive abilities of children who have survived near-drowning incidents may be masked by impairments that are primarily motoric, yet interfere with their ability to express their true cognitive

Received for publication 28 July 2017; Accepted 28 July 2017.
DOI: 10.1002/hbm.23760
Published online 00 Month 2017 in Wiley Online Library (wileyonlinelibrary.com).

potential. A follow-up study using diffusion techniques in the same population of children supported these findings, demonstrating that the prevalent insult is to motor regions, while other cerebral networks are relatively preserved (Ishaque et al., 2017). This adds further credence to the suggestion that these children may retain cognitive, perceptual, and emotional capabilities that they are unable to express through standard clinical measures of (motor) responsivity. Ultimately however, this possibility remained speculative in the absence of supporting functional data.

In the current study, Ishaque and colleagues took that extra step, using fMRI to examine preserved and disrupted resting state networks in pediatric survivors of near-drowning incidents (Ishaque et al., 2017). In this context, resting state fMRI is not only the paradigm of choice, but the paradigm of *necessity,* as traditional, task-activation fMRI has proven to be extremely difficult to implement reliably after pediatric brain injury (Herzmann et al., in press). Unlike the traditional approach to behavioral assessment in adult DOC patients, quantitative behavioral assessments were obtained via structured interviews with families and caregivers using Likert-style questionnaires developed specifically for this population of patients. This is important because families typically have knowledge of the patients' premorbid personalities, habits and preferences and are often the first to recognize subtle signs of awareness in patients diagnosed as DOC (Owen 2017).

In line with the hypothesis based on their previous structural imaging studies (Ishaque et al., 2016, 2017), basal ganglia and cerebellar (e.g., motor) resting state networks were most severely compromised in the patients, both group-wise and individually, concordant with the prominent motor deficits observed in these individuals behaviorally. Perceptual (visual, auditory, sensorimotor) and cognitive networks were strikingly preserved, including the default mode network and those reflecting fronto-parietal (or "executive" function), and the degree of preservation correlated significantly with the quantitative behavioral assessments, despite the relatively small sample size.

As a triad, these three papers add to the growing list of studies showing that after severe brain injury, standard clinical and behavioural assessment falls short of providing an accurate and compete diagnosis in many patients deemed to be in "the gray zone" between full consciousness and brain death (Owen, 2017). As the authors note, "children with anoxic brain damage are frequently deemed to be in a minimally conscious or vegetative state, but these determinations may well be flawed, as communication and task-cooperation limitations often preclude reliable assessment of cognitive status." Since the mid 1990s, functional neuroimaging in adult DOC patients has largely overturned the existing clinical malaise that had blighted progress in understanding these challenging and complex conditions for more than half a century (e.g. Fernández-Espejo et al., 2015; Naci et al., 2014; Owen et al., 2006). By combining state-of-the-art imaging with a novel approach to behavioral assessment, these recent findings suggest a way forward for the same to be achieved in children.

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