Finally, the degree of functional improvement observed after therapeutic injection of recombinant IL4I1 in EAE was moderate. The emphasis on IL4I1 as a preclinical treatment that reduces clinical disability, while suppressing myelin phagocytes attacking myelin sheaths in the CNS (Tannahill et al., 2015), while peripheral adaptive immune responses are minimal, and the repurposing of molecules or principles that are efficacious in RRMS for the treatment of SPMS has yet to prove successful (Mallucci et al., 2015).

In conclusion, whilst this work provides compelling evidence that IL4I1 reduces T cell expansion in a way that supports OPC survival and remyelination in vivo, more work is required to understand its precise mechanism of action, the therapeutic niche of this novel molecule, and to fully assess its functional impact in animal models of progressive multiple sclerosis.

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References


Default mode network, connectivity, traumatic brain injury and post-traumatic amnesia

This scientific commentary refers to ‘Disconnection between the default mode network and medial temporal lobes in post-traumatic amnesia’, by De Simoni et al. (doi:10.1093/brain/aww241).

In the individual who has sustained a traumatic brain injury (TBI), three clinical metrics are typically ascertained: the presence and duration of post-traumatic amnesia (PTA), whether loss of consciousness occurred, and a score on the Glasgow Coma Scale. These common metrics are used to determine injury severity and to triage the patient, without particular reference to what the underlying neuropathology might be. Previous neuroimaging studies have attempted to identify particular patterns of lesions or abnormalities associated with each of these metrics; however, efforts have generally been unsuccessful because the research has been limited by a focus on lesion type, location and/or burden, and has typically involved only a single imaging modality. A more contemporary approach is to examine the patient with multiple types of imaging and image analysis methods to explore not so much the location of identifiable lesions, but how brain networks and systems have been altered by the injury (Aerts et al., 2016; Hayes et al., 2016). Advanced neuroimaging methods have revolutionized how brain
networks can be functionally and structurally assessed in neurological disease and disorder (Glasser et al., 2016). Using such techniques in this issue of Brain, De Simoni and co-workers provide a compelling demonstration that a functional and structural disconnection between attentional and memory networks and the default mode network (DMN) forms at least part of the pathophysiological basis of PTA (De Simoni et al., 2016). The techniques used in the De Simoni et al. investigation reveal the effectiveness of a multimodal approach to neuroimaging assessment of TBI and provide a roadmap for future methods to better understand how brain injury disrupts brain networks.

Housed within the medial temporal lobe (MTL), the hippocampus has a well-established role in memory processing. As such, traumatic injury to the MTL has been assumed to play a major role in PTA—but this assumption has been based on inference. That MTL pathology somehow contributes to PTA seemed intuitive, requiring no further explanation. It made sense that TBI should affect the MTL, which lies adjacent to the tentorium cerebelli. Indeed, in a structural MRI study in which hippocampal volume was measured in patients with moderate-to-severe TBI, Brezova et al. (2014) found that those with PTA lasting more than 2 weeks had the most prominent hippocampal atrophy. However, there were also TBI patients who had PTA for up to 2 weeks post-injury, but who exhibited no hippocampal atrophy. This suggests that something other than just MTL pathology underlies the development of PTA. Furthermore, PTA also occurs in TBI patients with mild and moderate range Glasgow Coma Scale scores, in whom structural imaging reveals no visible abnormalities in the MTL or other regions of the brain.

Network damage in TBI is not a new topic (Ruppin and Reggia, 1995). In the broader discussion of amnesia, earlier arguments have been made about network damage as the basis for PTA. For example, over three decades ago, Markowitsch (1984) argued that while a specific lesion could result in PTA, the disorder occurred more often as a result of network disruption. But until recently there were no methods to assess network damage. By the beginning of the 20th century, histological staining techniques along with meticulous blunt dissection methods had outlined the major pathways and fasciculi of the human brain, including the pathways associated with the MTL. All 20th century neuroanatomy and neurology texts illustrated these pathways and presumed networks, with conjecture on their role in generating behaviour.

Figure 1  The fibre tracts of the default mode network are vulnerable to the effects of traumatic brain injury. (A) Dorsal view, using the output from a FreeSurfer (https://surfer.nmr.mgh.harvard.edu) based segmentation routine, of the cortical surface of the right hemisphere of a healthy adult. Extracted from diffusion tensor imaging (DTI)-based tractography in the same individual are some of the major tracts within the left hemisphere, including the location of the cingulum bundle (black arrows). Conventional colour coding for all DTI images applies where warm colours (orange-red) reflect lateral projecting tracts, blue vertically oriented tracts and green, DTI tracts oriented in the anterior-posterior plane. A movie file of the DTI is available online (Supplementary Video 1). (B) Primary tracts projecting across the corpus callosum with the black arrow pointing to those that project into the temporal stem and interface with the MTL, including projections that come from the cingulate. (C) DTI tractography depicting callosal and non-callosal fibre tracts of the right hemisphere, with the same bidirectional arrows reflecting the DMN as in (D). The upper arrows depict general connectivity between the frontal and parietal lobes, while the lower arrows depict connectivity between the parietal and temporal lobe regions. Note the intermingling of anterior-posterior oriented tracks with those that are vertically oriented. (D) Three-dimensional view of the brain isolating the hippocampus (yellow) and amygdala (purple) of the MTL of the left hemisphere, depicting their relative positions within the left hemisphere and their relation to the lateral ventricle (blue). The thalamus (brown), putamen (light brown) and caudate (green) are also shown. The DMN is depicted as a mustard splotch in the medial frontal, parietal and temporal lobes. The bidirectional arrows show the interactive connectivity within the DMN. Interactive pdfs derived from the FreeSurfer platform are available online (Supplementary Figs 1 and 2). (E) Taken from Hernandez et al. (2015). Regions where peak principle strain occurred during TBI that resulted in loss of consciousness (LOC). Data were obtained using instrumented mouth guards that permit extraction of peak strain effects. Used with permission from Springer.
and cognition. However, several major developments over the last two decades have made it possible to assess network integrity directly. The Human Connectome Project (Sporns et al., 2005) uses diffusion tensor imaging as its centrepiece method combined with task-based and resting state functional MRI. In these analyses, what is important is not just whether there is a loss of volume or a change in shape of a given region of interest, but how that region of interest is connected and the integrity of those connections with other components of the network. Diffusion tensor imaging methods provide direct measures of white matter integrity and structural connectivity, but functional MRI techniques permit assessment of the physiological patency of connections. Combining these techniques with typical lesion identification and morphological analyses provides a much more comprehensive approach for assessing the effects of TBI.

Understanding TBI begins with understanding the vulnerability of white matter and the consequences of traumatic axonal injury, including diffuse axonal injury (Buki and Povlishock, 2006). Diffusion tensor imaging has proven to be an excellent method for detecting white matter pathology in TBI (Hayes et al., 2016). Biomechanical studies of brain deformation using finite element modelling combined with MRI-derived modelling of brain structure and pathways has revealed the selective vulnerability of several critical pathways, especially those with long-coursing and interhemispheric projections (Fig. 1A–C).

The ability to detect what the brain does at rest has greatly advanced our understanding of brain networks and the neuroanatomical basis of cognition. In 1997, activation of a specific network—now known as the DMN—was reported at the point of task disengagement as the individual being scanned moved toward ‘quiet repose with eyes closed or simple visual fixation’ (reviewed in Raichle, 2015). This network has become the focus of intense interest as part of efforts to understand the memory and attentional deficits that feature in many neurological and neuropsychiatric disorders. Three interconnected cortical areas within each hemisphere, bilaterally connected via the corpus callosum, participate in the DMN including the medial and lateral parietal, medial prefrontal, and medial and lateral temporal cortices (Fig. 1D).

The different lobular areas within the DMN interconnect via white matter tracts that are long, making them vulnerable to the varied deformation effects associated with head trauma (Fig. 1). Returning to the finite element modelling and biomechanical depiction of common regions of brain deformation in TBI (Hernandez et al., 2015 and Fig. 1E), it is clear that the structures and pathways that make up the DMN all fall within the areas that experience the greatest strain effects during TBI. The long-coursing parietal-frontal and parietal-temporal pathways are particularly vulnerable, along with the interhemispheric connections.

Disruption of structural or functional integrity anywhere within the DMN is likely to impair attention and memory, but De Simoni et al. show that at least in their cohort of TBI patients, abnormal functional connectivity between the parahippocampal gyrus and posterior cingulate cortex contributes most to PTA. De Simoni et al. also demonstrate that the strength of this functional connectivity correlates with memory performance and speed of information processing, and that it changes over time as PTA subsides, further implicating it in PTA.

The DMN is but one network and there is much to learn about how individual networks interface with one another to generate whole-brain function. The white matter pathways connecting the limbic structures of the DMN overlap with those associated with other aspects of memory function and emotion regulation. The approach used by De Simoni et al. should be applied to assess functional connectivity within and between other networks assumed to be affected by TBI. As De Simoni et al. demonstrate, the DMN is dynamic and changes over time. Future studies need to continue with this line of prospective analysis, examining network perturbation and resiliency as the TBI patient transitions from acute to chronic stages.

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What is the role of TDP-43 in C9orf72-related amyotrophic lateral sclerosis and frontotemporal dementia?

This scientific commentary refers to "Timing and significance of pathological features in C9orf72 expansion-associated frontotemporal dementia", by Vatsavayai et al. (doi:10.1093/brain/aww250).

The C9orf72 hexanucleotide repeat expansion mutation is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), accounting for up to 12% of all patients in an average ALS clinic population. At post-mortem, patients with the C9orf72 hexanucleotide repeat expansion have the typical pathology seen in sporadic ALS and FTD, in which transactive response DNA-binding protein of 43 kDa (TDP-43; encoded by TARDBP) is translocated from its normal nuclear location to form cytoplasmic aggregates. However, they also show additional pathological features in the form of RNA foci, containing the transcribed hexanucleotide repeats, and aggregates, which stain with antibodies against dipeptide repeat proteins, the product of non-ATG translation. The order in which these distinct molecular abnormalities develop, and whether each of these pathological features is a necessary or sufficient condition for the development of clinical disease, are currently key questions in ALS/FTD research. In this issue of Brain, Vatsavayai et al. describe two strikingly different pathological cases of C9orf72-positive FTD with excellent ante-mortem characterization that provide novel and provocative contributions to this debate (Vatsavayai et al., 2016).

Transcription of the C9orf72 hexanucleotide repeat expansion can be detected as sense and antisense RNA foci in the nucleus and cytoplasm. Despite being located in the non-coding region of the C9orf72 gene,