

Cerebral activation of attention and working memory in traumatic brain injury

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List of abbreviations

A'	A-prime
ACC	anterior cingulate cortex
ADHD	attention-deficit/hyperactivity disorder
aI	anterior insula
BOLD	blood-oxygen-level-dependent
CSTC	cortico-striatal-thalamo-cortical
DAI	diffuse axonal injury
dIPFC	dorsolateral prefrontal cortex
DMN	default mode network
fMRI	functional magnetic resonance imaging
ldIPFC	left dorsolateral prefrontal cortex
mTBI	mild traumatic brain injury
NIBS	non-invasive brain stimulation
Pre-SMA	pre-supplementary motor cortex
rIFG	right inferior frontal gyrus
rs-fMRI	resting state functional magnetic resonance imaging
rTMS	repetitive transcranial magnetic stimulation
SN	salience network
SST	stop signal task
SSRT	stop signal reaction time
STN	sub-thalamic nucleus
TBI	traumatic brain injury
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation
TPJ	temporo-parietal junction
WM	working memory

Introduction: Executive dysfunction in traumatic brain injury

Traumatic brain injury (TBI) is a leading cause of neurological morbidity and mortality worldwide (Johnson, DeMatt, & Salorio, 2009). Its incidence is greatest in childhood and early adult life (> 640/100,000 children and young people less than 24 years of age each year) (FitzGerald, Tippet, Schuetz, & Pollard, 2008). Following a TBI, significant problems with memory, learning, and attention may arise, leading to life-long impacts on academic achievement, ability to secure employment, socio-emotional outcomes, and quality of life in over 30% of patients (Sigurdardottir, Andelic, Roe, & Schanke, 2009).

Traumatic brain injury results in large-scale disruption and impairment of brain networks, leading to significant functional impairments. These brain networks offer an insight into the interconnected, organized areas of the brain, which integrate locally and distally via axons and white matter tracts. This complex system of networks has been termed the “connectome” and underpins the link between brain activity and behavior (van den Heuvel & Sporns, 2011). The hallmark of TBI is axonal injury (focal or diffuse) and white matter tract injury. This injury results in brain network disruption with long-range disconnections and impaired brain network connectivity (Fagerholm, Hellyer, Scott, Leech, & Sharp, 2015; Sharp, Scott, & Leech, 2014). Axonal injury leads to poor outcomes, even where cortical damage is minimal (Sharp et al., 2014). Whereas injury to focal brain regions correlates poorly with outcome, connectome disruption can more accurately predict function across a range of injury severities and pathologies (Fagerholm et al., 2015). The most well studied brain networks are the seven intrinsic connectivity networks including the default mode network (DMN) and salience network (SN) (Bonnelle et al., 2011). To understand the effect of this network impairment it is important to understand how the functions of attention and working memory (WM) are governed.

The neural basis of attention and working memory

Attention and working memory are supported by rich, interconnected neural networks which rapidly mature between early childhood and early adulthood. The neural attention system involves three major components: alerting, orienting, and executive attention. Alerting involves involuntary capture of attention by salient (i.e., “attention-capturing”) stimuli and is functionally associated with the fronto-parieto-thalamic network and thalamus. Orienting refers to both the voluntary or involuntary movement of attention to a stimulus (Vossel, Geng, & Fink, 2014). Voluntary, or endogenous orientation of attention, is facilitated by the dorsal attention network (Fig. 1), which involves the frontal eye fields and parietal areas; whereas involuntary, or exogenous movement of attention, engages the ventral attention network, involving the temporo-parietal junction (TPJ) and the inferior frontal gyrus (Vossel et al., 2014). Executive control of attention will be discussed in the section below.

Much of our knowledge about the neurobiological underpinnings of attention is due to advances in modern neuroimaging techniques. Functional neuroimaging provides insight into brain activity and network interaction during attention and memory tasks, allowing acquisition of robust evidence in both clinical and healthy populations. Task-based functional MRI (fMRI) provides insight into changes in cortical activations during cognitive tasks, such as those related to attention and WM. Conversely, resting state fMRI (rs-fMRI) provides a measure of cortical activation when the brain is at rest (e.g., eyes closed). Generally, fMRI is a non-invasive assessment of changes in neural activity which uses the blood-oxygen-level-dependent (BOLD) signal to infer changes in neural activation with excellent spatial resolution. It is also a useful tool for probing dynamic patterns of connectivity (Iyer et al., 2019).

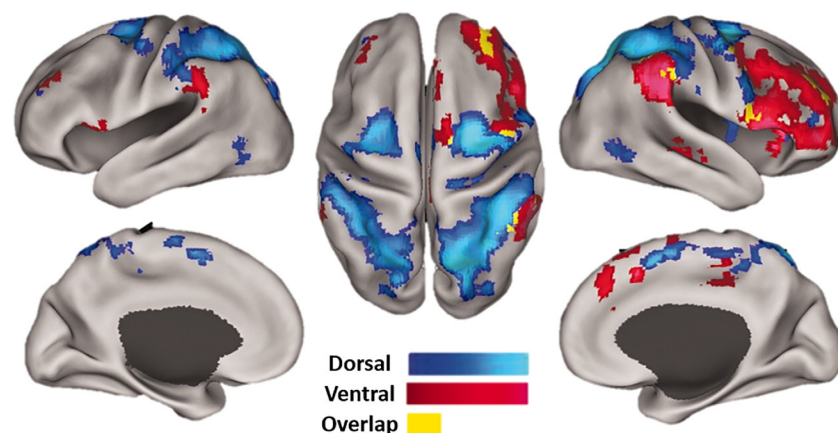


FIG. 1 Dorsal (blue) and ventral (red) attention networks and the overlap between them (yellow). Data are displayed on the lateral and medial surfaces of the left hemisphere (left), the dorsal surface (center), and the lateral and medial surfaces of the right hemisphere (right). Adapted from Fox, M. D., Corbetta, M., Snyder, A. Z., Vincent, J. L., & Raichle, M. E. (2006). Spontaneous neuronal activity distinguishes human dorsal and ventral attention systems. *Proceedings of the National Academy of Sciences of the United States of America*, 103 (26), 10046–10051. Copyright (2006) National Academy of Sciences, U.S.A.

The dual-network model of attention

As the third major component of attention, executive control of attention refers to the top-down mode of attentional control. The executive network features both cingulo-opercular and fronto-parietal areas (Konrad et al., 2005), which act together in a dual-network architecture. Cingulo-opercular components such as the anterior cingulate cortex and anterior insula (aI) maintain focus during tasks; whereas fronto-parietal components, including the dorsolateral prefrontal cortex (dlPFC), initiate and adjust attentional control (Fig. 2) (Dosenbach, Fair, Cohen, Schlaggar, & Petersen, 2008).

The cingulo-opercular network, also referred to as the salience network, is engaged during behavioral tasks requiring sustained attentional focus and response to salient stimuli. The fronto-parietal network, in contrast, is more strongly engaged during tasks which require a more top-down control of inhibition. The inhibitory component of attention has been found to be a central deficit in TBI (Dosenbach et al., 2008).

It is important to acknowledge another important network which mediates attentional response, known as the default mode network. This network is a task-negative network (or “resting state” network), which is normally activated during internally focused attention (i.e., introspection, mind-wandering) and deactivated during the external focus of attention (e.g., during inhibition and working memory tasks described in this chapter) (Raichle, 2015). The DMN consists primarily of the posterior cingulate cortex, retrosplenial cortex and ventromedial prefrontal cortex (Sharp et al., 2011). Previous evidence has indicated that deactivation of this network is important for mental effort in cognitive tasks (Li, Yan, Bergquist and Sinha, 2007). The DMN will be discussed in more detail in later subsections of this chapter.

Inhibitory control

Inhibitory control relates to the ability to engage in an appropriate response while suppressing a more dominant but less appropriate response. For example, this might involve a person focusing on a task while resisting the urge to check their mobile phone. As a hub in both the cingulo-opercular and fronto-parietal networks, the dlPFC is thought to play an overarching role in the control of inhibition (Chabran et al., 2020; Peters, Dunlop, & Downar, 2016). Inhibition can be broken down into the two domains of *reactive* and *proactive* inhibition:

- *Reactive* inhibition refers to the cue-triggered stopping of a response which has already been initiated. It generally only occurs in close temporal proximity of a presented cue (i.e., it is usually a direct effect of the cue) (Aron, 2011). A common measure of reactive inhibition is the Stop Signal Reaction Time (SSRT) of the Stop Signal Task (SST), where

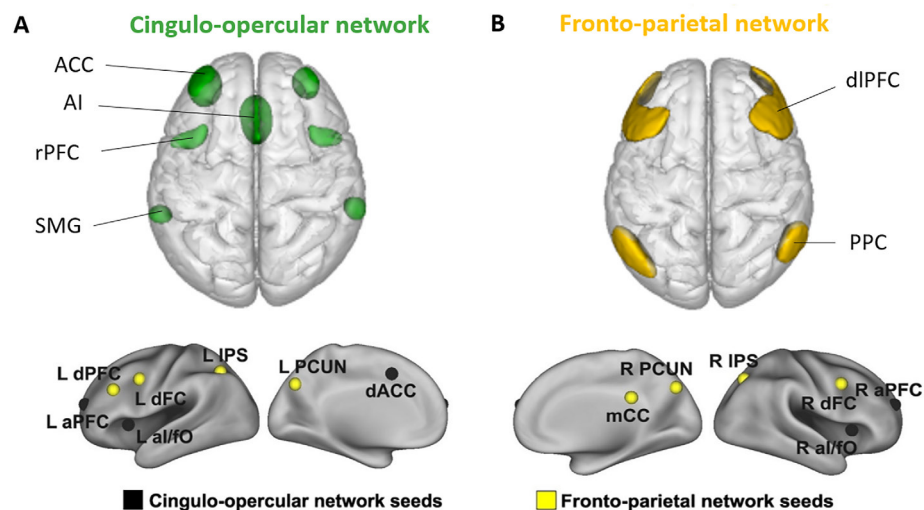


FIG. 2 Diagram representing (A) cingulo-opercular and (B) fronto-parietal networks in healthy participants. These two networks are implicated in the control of attention. L, left; R, right; aPFC, anterior prefrontal cortex; aI, anterior insula; dlPFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; IPL, intraparietal lobule; PCUN, precuneus; IPS, intraparietal sulcus; AI, anterior insula; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; SMG, supramarginal gyrus; mCC, middle cingulate cortex; fO, frontal operculum. Adapted from Chabran, E., Noblet, V., de Sousa, P. L., Demuyne, C., Philippi, N., Mutter, C., ... Blanc, F. (2020). Changes in gray matter volume and functional connectivity in dementia with Lewy bodies compared to Alzheimer's disease and normal aging: Implications for fluctuations. *Alzheimer's Research Therapy*, 12 (1), 1–13; Han, K., Chapman, S. B., & Krawczyk, D. C. (2018). Neuroplasticity of cognitive control networks following cognitive training for chronic traumatic brain injury. *NeuroImage: Clinical*, 18, 262–278. Creative Commons CC-BY.

a longer reaction time may indicate deficits in reactive inhibition. Reactive inhibition is mediated by *direct* communication of the pre-supplementary motor area (pre-SMA) and right inferior frontal gyrus (rIFG) with the sub-thalamic nucleus (STN) of the basal ganglia (Fig. 3), allowing a quick response.

- *Proactive* inhibition, on the other hand, is a preparatory process which controls the initial instigation of the response. A variety of sensory, cognitive and limbic sources influence proactive inhibition even before presentation of a cue (Aron, 2011). Akin to reactive inhibition processes, proactive inhibition involves communication between the pre-SMA and rIFG. In proactive inhibition, however, these regions then send signals via an *indirect* pathway to the striatum or STN to the output nuclei of the basal ganglia (Fig. 3). Proactive inhibition can be measured using reaction time of tasks involving a “go” trial, such as the “go” component of the Go/No-Go or Stop-Signal tasks (Tan et al., 2019). Delayed response tasks can also be used to measure this type of inhibition, as they create conflicts in decision-making.

Reactive and proactive inhibitory functions improve with age. Young adults typically exhibit faster and more accurate responses on reactive inhibition tasks while displaying greater deactivation of the motor cortex. Proactive inhibition shows a similar developmental pattern, where compared to young children, young adults exhibit better response slowing in anticipation of stopping, alongside increased fronto-striatal connectivity (Vink et al., 2014).

Measuring inhibition

The Stop Signal Task is primarily a reactive inhibition task. It activates the cingulo-opercular network, where the rIFG and pre-SMA areas work in synchrony to inhibit a response, maintaining strong connections with the basal ganglia (Jahfari et al., 2011). The aI is an important node in the cingulo-opercular network, as it is responsible for (1) the maintenance of task-specific attention and (2) responding to salient stimuli (Dosenbach et al., 2007). Increased activation of the left

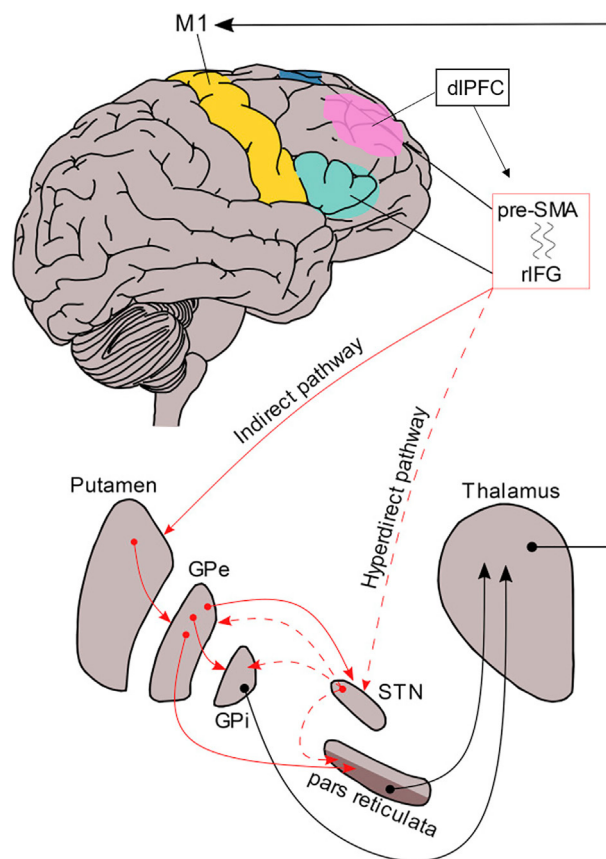


FIG. 3 Diagram representing indirect and direct (hyperdirect) pathway between pre-SMA/rIFG and basal ganglia. These pathways are implicated in reactive and proactive inhibition. M1, primary motor cortex; pre-SMA, pre-supplementary motor cortex; dlPFC, dorsolateral prefrontal cortex; GPe, external globus pallidus; GPi, internal globus pallidus. Adapted from Tan, J., Iyer, K. K., Tang, A. D., Jamil, A., Martins, R. N., Sohrabi, H. R., ... Fujiyama, H. (2019). Modulating functional connectivity with non-invasive brain stimulation for the investigation and alleviation of age-associated declines in response inhibition: A narrative review. *NeuroImage*, 185, 490–512. Copyright 2019 Elsevier.

aI has been associated with faster SSRTs (reflecting more efficient stopping) (Swick, Ashley, & Turken, 2011) (Fig. 4). Engagement in the SST is associated with deactivation of the DMN (Li, Yan, Bergquist and Sinha, 2007).

The bilateral dlPFC monitors inputs from interconnected areas such as the rIFG and pre-SMA during the selection of an appropriate response in the SST. The SST is predominantly associated with the activation of the left dlPFC (ldlPFC) compared to the right dlPFC. Here, the ldlPFC is thought to be more involved in analysis, planning, and attention disengagement; whereas the right dlPFC may be more responsible for integration of plans into a strategic sequence (Barbey, Koenigs, & Grafman, 2013).

As previously mentioned, the Go/No-Go task is primarily used to measure proactive inhibition. It is thought to involve neural mechanisms distinct from those activated during the SST (Swick et al., 2011). During the Go/No-Go task, participants must react to a “go” stimulus, and refrain from reacting to a “no-go” stimulus. Inhibition is often measured by the number of errors (or false alarms) a subject makes on “no-go” trials. The Go/No-Go task has been found to activate the pre-SMA, rIFG, bilateral inferior parietal regions, occipital regions, putamen and left premotor cortex (Simmonds, Pekar, & Mostofsky, 2008). These regions are part of the fronto-parietal network, which is involved in adaptive control (Swick et al., 2011). Similarly to the SST, performance of the Go/No-Go task is associated with deactivation of the DMN (Li et al., 2007).

In general, the distinction between the SST and Go/No-Go Task can be thought of as follows: whereas the SST requires participants to “stop,” the Go/No-Go task requires them to “not go.” In this sense, the SST is thought to more strongly engage the predominantly frontal cingulo-opercular network, and in comparison the Go/No-Go Task engages a wider fronto-parietal network (Swick et al., 2011).

Working memory

Working memory also plays a critical role in executive function and heavily engages prefrontal areas, such as the dlPFC, as well as other task-positive regions such as the premotor, dorsal cingulate, and lateral posterior parietal cortices (Owen, McMillan, Laird, & Bullmore, 2005). WM is a temporary, capacity-limited memory-holding store which is critical for executive function. It is related to attention in that it requires sustained attentional focus on task-relevant mental representations during inhibition of competing distractors. WM plays a crucial role in learning, therefore allowing an individual to manipulate and process information to be stored in long-term memory (Baddeley, 2012). It is commonly investigated using

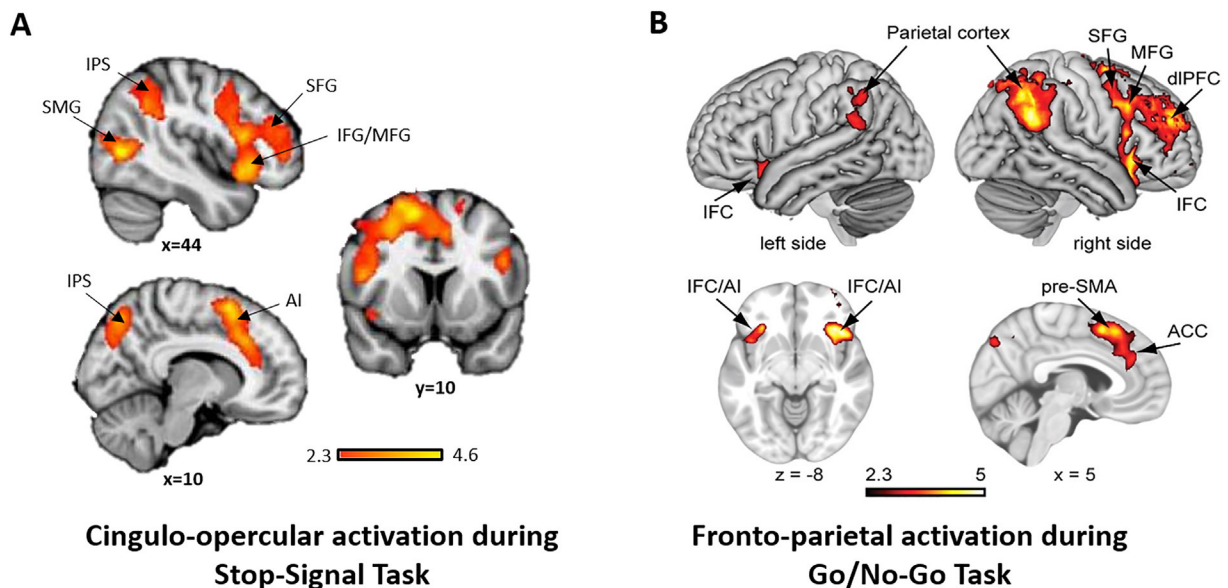


FIG. 4 Diagram representing activation of (A) cingulo-opercular network during Stop Signal Task and (B) fronto-parietal network during Go/No-Go Task in healthy participants. The cingulo-opercular and fronto-parietal networks are implicated differently in tasks requiring proactive and reactive inhibition. L, left; R, right; aPFC, anterior prefrontal cortex; aI, anterior insula; dlPFC, dorsolateral prefrontal cortex; IPL, intraparietal lobule; PCUN, precuneus; IPS, intraparietal sulcus; AI, anterior insula; SFG, superior frontal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; SMG, supra-marginal gyrus. Adapted from Sharp, D., Bonnelle, V., De Boissezon, X., Beckmann, C., James, S., Patel, M., & Mehta, M. A. (2010). Distinct frontal systems for response inhibition, attentional capture, and error processing. *Proceedings of the National Academy of Sciences of the United States of America*, 107 (13), 6106–6111; Van Gaal, S., Ridderinkhof, K. R., Scholte, H. S., & Lamme, V. A. (2010). Unconscious activation of the prefrontal no-go network. *Journal of Neuroscience*, 30 (11), 4143–4150. Copyright 2010 Society for Neuroscience.

the *n*back task, which is associated with activation of the dlPFC (a hub for prefrontal WM-related activation) and deactivation of the DMN (Owen et al., 2005).

Developmental changes in brain networks

Traumatic brain injury is a common diagnosis in children and adolescents, where 691 children per 100,000 are treated for the condition merely in emergency departments each year (Thurman, 2016). Therefore, understanding the developmental changes which occur in the executive network throughout childhood and adolescence is important in the treatment of TBI-related deficits. Beginning in infancy and extending into childhood, there is a rapid anatomical brain volume increase, cortical thickening and surface expansion, formation of new synapses, and myelination (Hagmann et al., 2010). This maturation of attention and WM-related functions is associated with several factors which are summarized below. It is important to consider TBI-related deficits discussed in this Chapter in the context of these developmental changes.

Maturation of attention networks

Maturation of the central executive network from childhood into adulthood is characterized by increasingly focal and anterior activation, including distinct developmental trajectories in attention networks (Fig. 5) (Sherman et al., 2014). From around 4 years of age, the executive attention network gradually differentiates from orienting and alerting systems

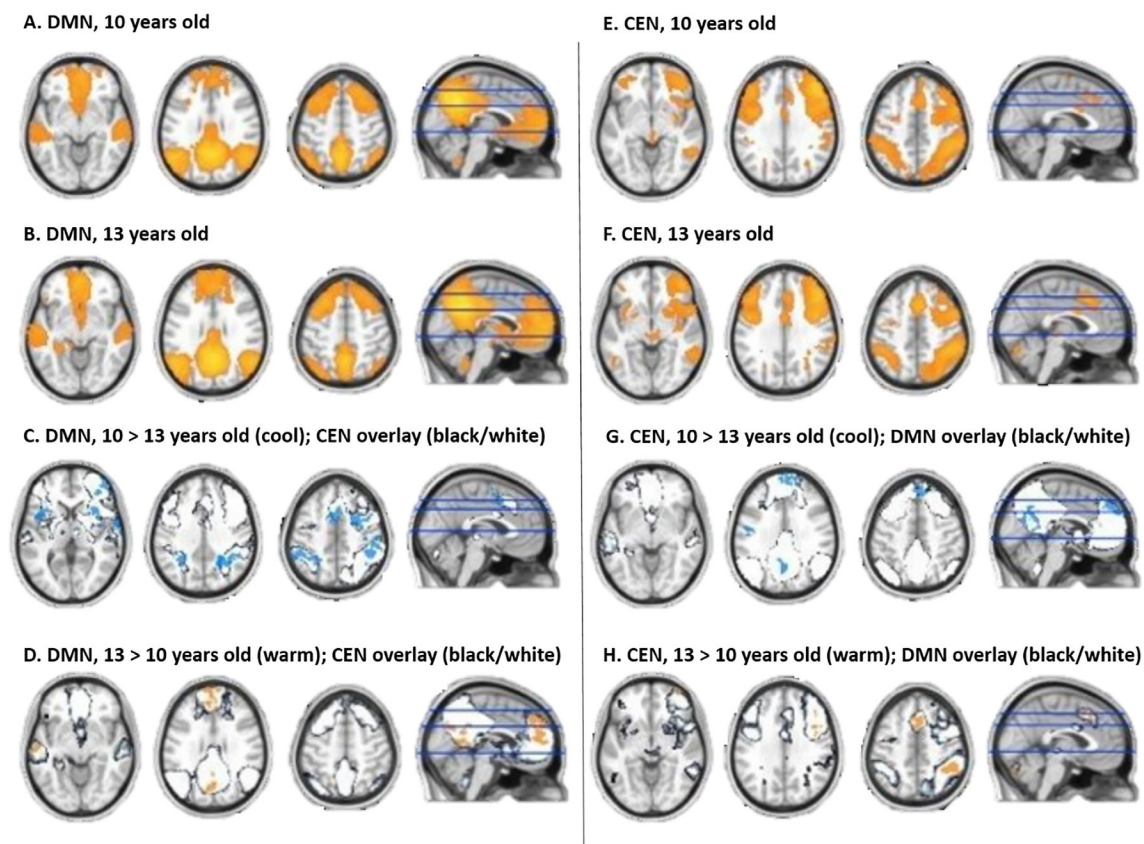


FIG. 5 Default mode network (DMN) and central executive network (CEN) connectivity maps at ages 10 and 13 in healthy participants while listening to a stream of nonsense speech. Overall, children display more focal and anterior activation at 10 years compared to at 13 years of age. Panels represent (A and B) connectivity maps for DMN at 10 and 13 years of age, respectively; (C) DMN-seed connectivity which was higher at 10 than 13 years of age (cool) and (D) DMN-seed connectivity which was higher at 13 than 10 years of age (warm), both overlaid on the 13 year CEN connectivity map (black and white); (E and F) connectivity maps for CEN at 10 and 13 years of age, respectively; (G) CEN-seed connectivity which was higher at 10 than 13 years of age (warm) and (H) CEN-seed connectivity which was higher at 13 than 10 years of age (warm), both overlaid on the 13 year DMN connectivity map (black and white). Imaged adapted from Sherman, L. E., Rudie, J. D., Pfeifer, J. H., Masten, C. L., McNealy, K., & Dapretto, M. (2014). Development of the default mode and central executive networks across early adolescence: A longitudinal study. *Developmental Cognitive Neuroscience*, 10, 148–159. Copyright 2014 Elsevier.

to become the dominant factor of cognitive control and self-regulation. As a critical component of executive attention, the anterior cingulate cortex (ACC) is thought to be especially implicated in these changes, becoming increasingly differentiated from the orienting network during maturation of sustained attention throughout childhood and into late adolescence (Fair et al., 2009).

Maturation of inhibition

Children are more susceptible to distraction than adults, and yet are also less able to disengage attention (Konrad et al., 2005). The maturation of inhibition in children shows a similar pattern to that of sustained attention; maturing throughout childhood and into late adolescence. This is reflected by changes in intrinsic brain networks. During inhibition tasks, younger children extensively recruit the middle and superior frontal gyri of the prefrontal cortex compared to older children and adolescents. In particular, recruitment of the left inferior frontal gyrus during the Go/No-Go task is decreased in adolescents when compared to adults (Vara, Pang, Vidal, Anagnostou, & Taylor, 2014). Over the course of development, inhibition-related activation becomes increasingly frontally-guided (Levin, Hanten, Zhang, Swank, & Hunter, 2004).

Maturation of working memory

Working memory function exhibits clear maturational changes across puberty, adolescence, and early adulthood. This maturation process is associated with increases in cortical activation in the middle frontal gyrus, and in particular, the dlPFC (Gogtay et al., 2004). In adults, WM-related activation involves several distinct frontal and temporal regions. The dlPFC is widely regarded as a core hub for WM-related processing. In addition to the dlPFC, visual WM tasks involving objects and faces activate areas of the inferior temporal/fusiform gyrus and middle occipital cortex; whereas WM tasks involving spatial and movement judgment activate the inferior parietal/occipital region, superior frontal sulcus and middle temporal region (Ciesielski, Lesnik, Savoy, Grant, & Ahlfors, 2006). Children recruit similar regions to adults during WM tasks, but display more variable and widespread brain activation. In general, the maturation of WM networks throughout childhood and into adulthood involves a shift from diffuse and dorsal activation, to focal and anterior activation (Scherf, Sweeney, & Luna, 2006).

Disruptions following TBI

Brain network disruption following TBI

The underlying neuroanatomical and physiological changes, which occur following TBI, are also important in understanding deficits in executive functioning and brain network activity. TBI results in axonal injury and damage to white matter tracts, thus affecting network connectivity (Fig. 6) (Maria et al., 2019). This axonal injury and white matter tract disruption causes damage to brain networks involved in attention and WM. These changes in network connectivity are particularly important in childhood TBI, where they occur in the context of marked developmental and plasticity changes. As a result, damage acquired at a young age may become ingrained over time during maturation and development, which may result in aberrant structural and functional connectivity throughout childhood and adolescence (Maria et al., 2019).

TBI also causes disruptions in the small-world architecture of the brain. "Small-world" connectivity relates to normally highly connected local modules involved in specialized processing. Following TBI, small-world architecture of the brain is impacted, resulting in overall decreases in functional connectivity and reduced network efficiency. The resultant overall weaker global integration of brain networks in TBI is thought to decrease capacity to integrate information across various brain regions and networks (Caeyenberghs et al., 2014).

Deficits in attention and inhibition following TBI

Attention problems are the most common deficit reported following TBI, with a study finding that 14% of patients experience new-onset attention problems at 1, 4, and 10 months post-TBI (Hooper et al., 2004). Attention is a vital component of learning and memory which allows for the filtering and selection of salient stimuli during inhibition of less important stimuli. Deficits in attentional functions including focused, sustained, divided, alternating and selective attention, as well as response inhibition are common sequelae after TBI (Konrad, Gauggel, Manz, & Schöll, 2000). These deficits are similar to those seen in ADHD, creating an interesting link between the two conditions.

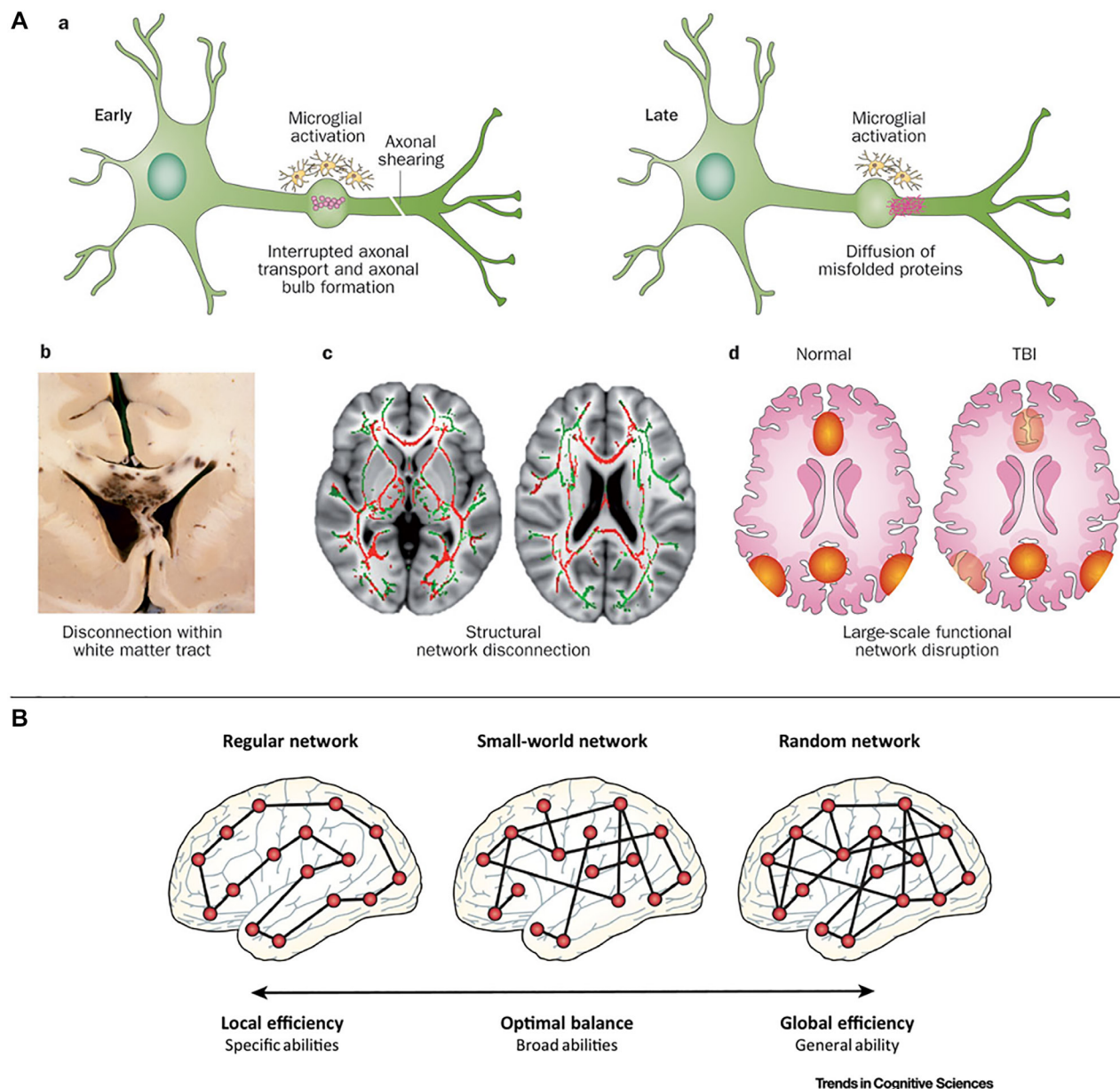


FIG. 6 (A) Traumatic brain injury-related damage across different spatial scales. (a) Diffuse axonal injury can interrupt neuronal processes and trigger neuroinflammation; (b) injuries may be apparent in large-scale white matter tracts, including the corpus callosum (pictured); (c) long distance communication is interrupted following TBI-related damage, often resulting in reduced fractional anisotropy (red, white matter skeleton; green, intact structure); (d) white matter damage can affect nodes within brain networks (default mode network pictured). (B) Small-world network balance between local and global efficiency. Image reused from Sharp, D. J., Scott, G., & Leech, R. (2014). Network dysfunction after traumatic brain injury. *Nature Reviews Neurology*, 10 (3), 156. Retrieved from <https://www.nature.com/articles/nrneurol.2014.15.pdf>, Copyright 2014 Springer Nature and Barbey, A. K. (2018). Network neuroscience theory of human intelligence. *Trends in Cognitive Sciences*, 22(1), 8–20. Copyright 2018 Elsevier. TBI, traumatic brain injury.

Interestingly, children and adults sustaining a TBI have a 4–5 times greater risk of developing secondary ADHD compared to those without TBI. In fact, secondary ADHD following TBI has been found to occur in 20% of previously unaffected individuals (Schachar, Levin, Max, Purvis, & Chen, 2004). Individuals with ADHD are also more likely to engage in risk-taking behavior where traits of restlessness, inattentiveness and impulsiveness contribute to an increased propensity for accidents, which in turn increases the risk of TBI (Schachar et al., 2004). These functional attention deficits are reflected in structural and functional differences in frontal areas of the brain, which will be discussed later in this chapter.

Inhibition and the default mode network

Patients with TBI often exhibit abnormal default mode network activation during working memory or attention processes. Typically, the DMN exhibits reduced levels of activity during attentionally demanding tasks (Raichle, 2015) in healthy participants. In this sense, the DMN is described to be “anti-correlated” with attention and WM-related regions. Following TBI, abnormalities in DMN activation are common, primarily involving decreased anti-correlation between the DMN and executive areas, where the DMN is hyperactive (Fig. 7). This abnormal activation is termed “DMN interference”, due to its interfering effect on normal network operations. Further, damage within the cingulum bundle (an important salience network tract connecting the posterior cingulate and ventromedial prefrontal cortices) causes impairments in sustained attention and inhibition (Sharp et al., 2014). Of note, damage to a SN tract connecting the right aI to the midline pre-supplementary motor area-dorsal ACC strongly and specifically predicts a failure to appropriately deactivate the DMN (Sharp et al., 2014). Abnormal DMN function can be used as a sensitive marker of impairments of attention following TBI (Bonnelle et al., 2011, 2012).

The integrity of the salience network has been found to be an important indicator of inhibitory function in TBI patients and is measured via cognitive tasks such as the SST (Bonnelle et al., 2012). Typically, functional connectivity between the SN and DMN normally increases when motor responses are rapidly inhibited or changed, and the DMN normally shows reduced activity during stopping. However, following TBI, this transient functional connectivity increase is reduced, and the DMN fails to be deactivated (Fig. 8) (Bonnelle et al., 2012; Jilka et al., 2014).

After TBI, damage within the salience network is thought to impair coupling between the right aI and DMN (Jilka et al., 2014). The right aI seems to play an important role in the connectivity between the SN and DMN, where studies have found that the right aI exerts a causal influence on DMN activity across a range of behaviors (Sridharan, Levitin, & Menon, 2008). Disruptions in SN and DMN coupling are thought to affect cognitive control and attentional focus (Jilka et al., 2014). In particular, TBI sustained in childhood can disrupt the maturation of inhibitory networks, leading to long-term deficits (Levin et al., 2004).

Deficits in working memory following TBI

Working memory is important for a broad range of cognitive functions, acting as the interface between perception, long term memory and action (Fig. 9) (Baddeley, 2012). It is closely related to attentional function and is often impacted following TBI. Deficits in WM are seen across the spectrum of TBI severity, where patients find it more difficult to process greater cognitive loads compared to their uninjured counterparts (McAllister et al., 2001). This is thought to be due to disruptions

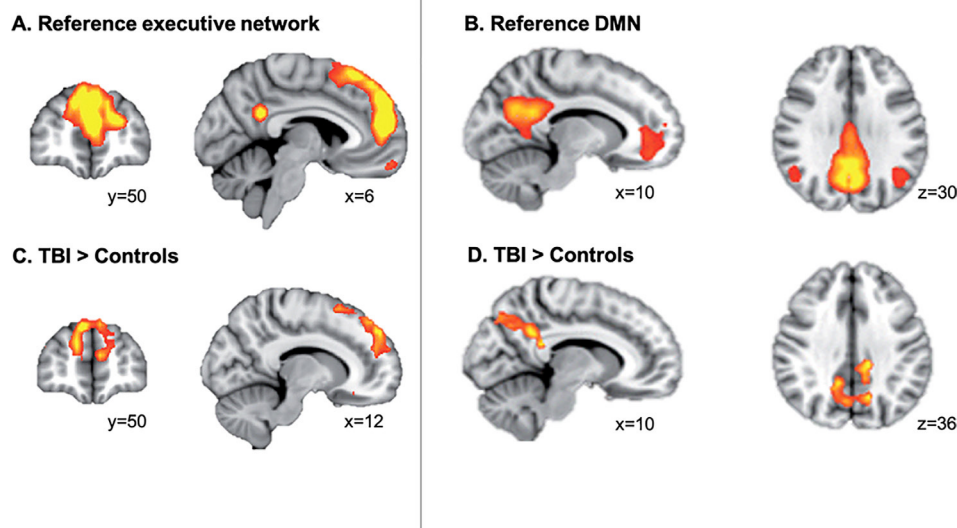


FIG. 7 Hyper-connectivity in TBI patients compared to controls. (A) Reference executive network connectivity; (B) Reference default mode network connectivity; (C) greater activation in executive network of TBI participants compared to controls; (D) greater activation in DMN of TBI patients compared to controls. TBI, traumatic brain injury; DMN, default mode network. Image reused from Sharp, D.J., Beckmann, C.F., Greenwood, R., Kinnunen, K.M., Bonnelle, V., De Boissezon, X., et al. (2011). Default mode network functional and structural connectivity after traumatic brain injury. *Brain*, 134 (8), 2233–2247. Copyright 2011 Oxford University Press.

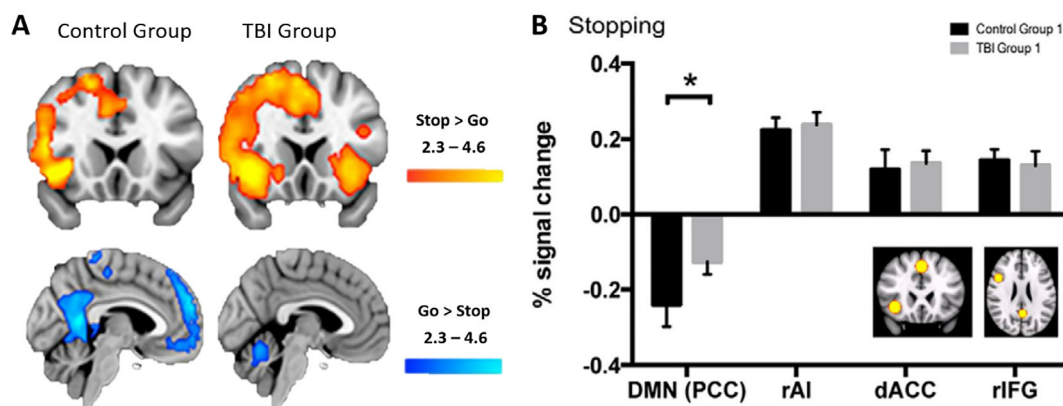


FIG. 8 Stop Signal task activation associated with correct stop vs go trials in control and TBI participants. Patients who have sustained a TBI experience abnormal default mode network connectivity during the stopping phase of the Stop Signal Task. Image adapted from Jilka, S. R., Scott, G., Ham, T., Pickering, A., Bonnelle, V., Braga, R. M., ... Sharp, D. J. (2014). Damage to the salience network and interactions with the default mode network. *Journal of Neuroscience*, 34 (33), 10798–10807. Copyright 2010 Society for Neuroscience.

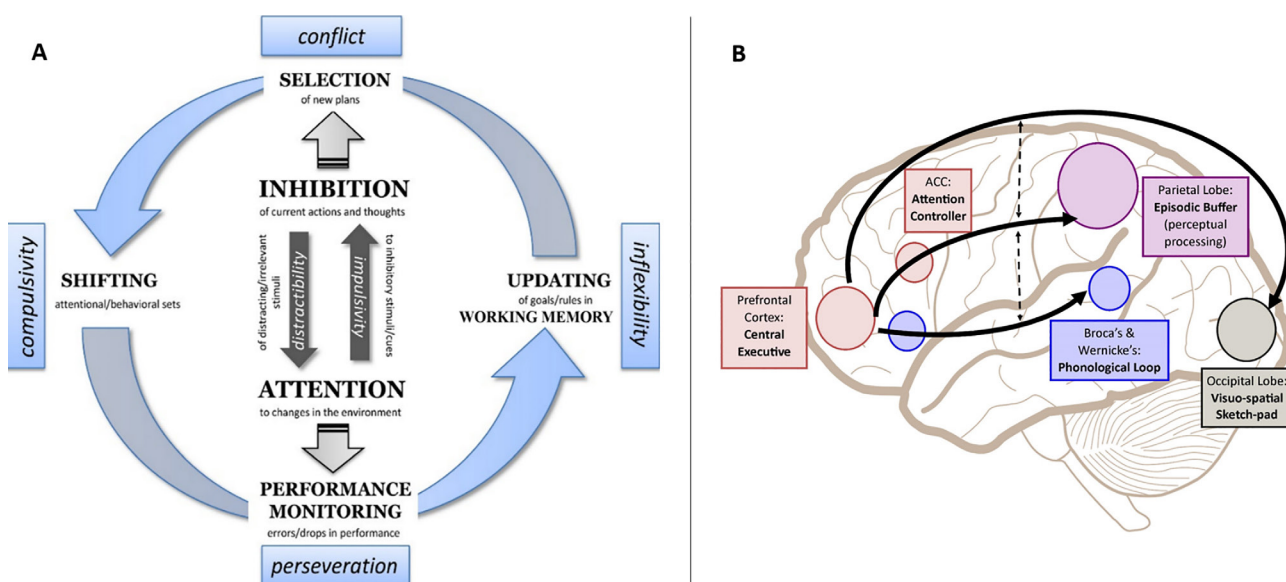


FIG. 9 Inter-relationships between executive functions including attention, inhibition, working memory, and interference control. (A) Schematic representation of the relationship between attention and working memory-related functions and (B) interplay between attention and WM superimposed on a brain template. Images adapted from Bari, A., & Robbins, T. W. (2013). Inhibition and impulsivity: Behavioral and neural basis of response control. *Progress in Neurobiology*, 108, 44–79. Copyright 2013 Elsevier, and Chai, W. J., Abd Hamid, A. I., & Abdullah, J. M. (2018). Working memory from the psychological and neurosciences perspectives: A review. *Frontiers in Psychology*, 9, 401. Retrieved from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5881171/pdf/fpsyg-09-00401.pdf>, Creative Commons CC-BY.

to the central executive network which impacts the brain's ability to allocate processing resources. These deficits are related to comorbid attention problems seen in TBI, where sustained attention and appropriate response inhibition must occur in order for working memory systems to function (McAllister, Flashman, Sparling, & Saykin, 2004).

As a hub for executive functioning, the prefrontal cortex (and in particular, the dlPFC) commonly shows abnormal WM-related activation following TBI. In mild TBI, evidence has shown that the dlPFC is hyperactive during working memory tasks (Hillary, Genova, Chiaravalloti, Rypma, & DeLuca, 2006). This hyper-activation is suggested to occur as a compensatory effort for a loss of processing efficiency due to DAI in various white matter tracts. This pattern has also been noted in moderate to severe adult TBI, where a study found that patients displayed greater bilateral activation while completing higher *n*back task cognitive loads compared to controls. In particular, moderate to severe TBI was related to activation of the aI (Kim et al., 2012). This evidence suggests that hyper-activation of WM-related areas in TBI may reflect network-wide damage.

Following TBI, the DMN often fails to deactivate during working memory tasks, similar to the abnormal coupling observed between areas of the salience and default mode networks during attention tasks (above). Studies have described abnormally increased DMN activation during a WM task following TBI in both children (Stein, Iyer, Khetani, & Barlow, 2021) and adults (Leech, Kamourieh, Beckmann, & Sharp, 2011). Functional connectivity studies have shown abnormally high posterior cingulate cortex connectivity within the DMN during WM tasks to be associated with more efficient response speeds, indicating its important role in cognitive recovery (Sharp et al., 2011). This decreased anti-correlation between WM and default mode-related areas seen in the chronic stage following TBI has been suggested as a compensatory mechanism during cognitive recovery, particularly in studies which find participants to have clinically normal working memory performance (Leech et al., 2011).

Structural and functional changes following TBI

Cortical thickness

In non-injured populations of both children and adults, attention and working memory functions are associated with cortical thickness of frontal and temporal areas, where increased cortical thickness in prefrontal regions is positively correlated with increases in both attention and WM functioning in children and adults (Merkley et al., 2008). Childhood TBI particularly impacts cortical thickness, where injuries can affect the development of brain regions, especially in frontal executive regions (Merkley et al., 2008).

Cortical-striatal loop

Previous evidence has indicated that changes in cortical thickness in TBI also has larger, network-wide effects, including in the cortico-striatal-thalamo-cortical (CSTC) loop. The CSTC loop is thought to be involved in attention-related dysfunctions following TBI. This loop features nodes of the cingulo-opercular (or salience) network including the dorsal ACC and bilateral aI; cortical nodes in the dlPFC and inferior parietal lobule; as well as a set of subcortical nodes in the head of caudate, medio-dorsal nucleus of the thalamus and the dopaminergic brainstem nuclei (Fig. 10). Damage to the CSTC loop has been found to impair cognitive control, including impulsivity, task-switching, and working memory processes (Peters et al., 2016).

Cortico-striatal-thalamo-cortical connectivity is implicated in both TBI and ADHD-related attention and working memory deficits. During the chronic (from approx. 6 months post-injury) stage of adult TBI, increased diffusion of water in the brain (indicative of white matter tract damage) in the bilateral orbitofrontal gyrus, insula and caudate nucleus is associated with impulsivity (Newcombe et al., 2011). This disruption of CSTC white matter networks following TBI results in decreased network efficiency, thus contributing to the clinical deficits seen in TBI (Caeyenberghs et al., 2014). However, there is limited evidence relating to the development of the CSTC loop in younger populations.

Abnormal thalamo-cortical activation has also been noted in ADHD populations. Given the correlation between these conditions, understanding thalamo-cortical activation in ADHD populations may provide insight into deficits following TBI. Stronger thalamo-putamen connectivity has been noted in children diagnosed with ADHD who have poorer working memory function (Mills et al., 2012). Conversely, weaker thalamo-cortical connectivity has been found in adults with persistent and remitted ADHD during a response preparation task (Clerkin et al., 2013). These differences between adult and child studies may indicate altered activation at different stages of development, highlighting the impact of attention deficits on large-scale brain networks. Taken together, this evidence suggests that the CSTC loop provides important insights into the impacts of ADHD and TBI-related attention deficits.

Modulating cortical activations in TBI using non-invasive brain stimulation

Over the past decades, non-invasive brain stimulation (NIBS) has emerged as a neuromodulatory technique which may aid recovery following TBI. The principle of NIBS is to activate or inhibit neural activity in targeted regions of the cortex to improve various functions, such as attention and working memory. NIBS may facilitate clinical recovery by modulating structural and functional interactions within the brain, strengthening synapses, and increasing the number and connections between dendritic spines (Nitsche et al., 2008).

Several studies have reported improvements in attention and WM processes following TBI using NIBS such as transcranial direct current stimulation (tDCS) or repetitive transcranial magnetic stimulation (rTMS) (Fig. 11) (Zaninotto et al., 2019). In particular, tDCS has been demonstrated to modulate both clinical (i.e., behavioral performance on

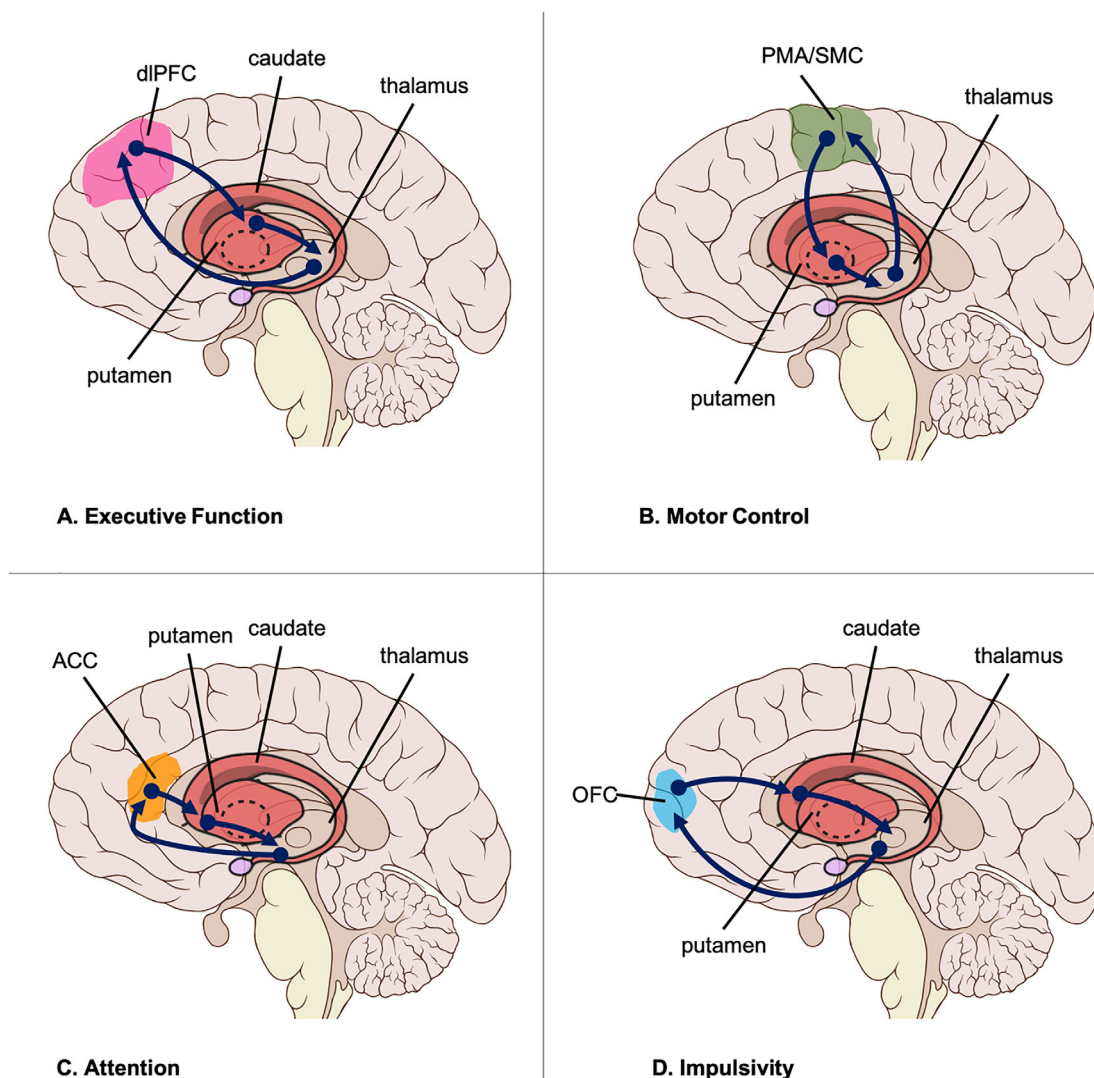


FIG. 10 Various components of the cortico-striatal-thalamo-cortical loop. This loop is implicated in attentional control, involving components related to (A) executive function; (B) motor control; (C) attention; and (D) impulsivity. dIPFC, dorsolateral prefrontal cortex; PMA/SMC, primary motor cortex/supplementary motor cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex. Image is original work with brain template by Patrick J. Lynch; C. Carl Jaffe.

executive tasks) and neurophysiological measures (i.e., fMRI and EEG) when applied during a cognitive task. A potential strength of tDCS in the context of TBI is the indirect nature of current flow in this technique. Given that TBI is a diffuse injury, tDCS may be a useful clinical tool, as the large spatial extent of current flow conferred in this technique may work to address larger areas of diffuse injury in TBI (Fig. 11). Thus, further research is warranted for tDCS in TBI populations. In contrast, rTMS has also been investigated to improve cognitive deficits in TBI. rTMS directly modulates synaptic firing, and therefore can more directly affect brain activity compared to tDCS. Some evidence suggests that rTMS may produce sustained improvement (up to several months) in ongoing symptoms following injury. However, rTMS poses some safety concerns in TBI populations due to its neural excitatory effects which confer a possible seizure risk.

Future neurorehabilitation approaches using NIBS in TBI should address the heterogeneity of injury and resulting variability in patient response to NIBS, for example, through the use of neuroimaging. As such, future research should aim to examine how individual differences in injury affect responses to NIBS, allowing “personalization” of treatment.

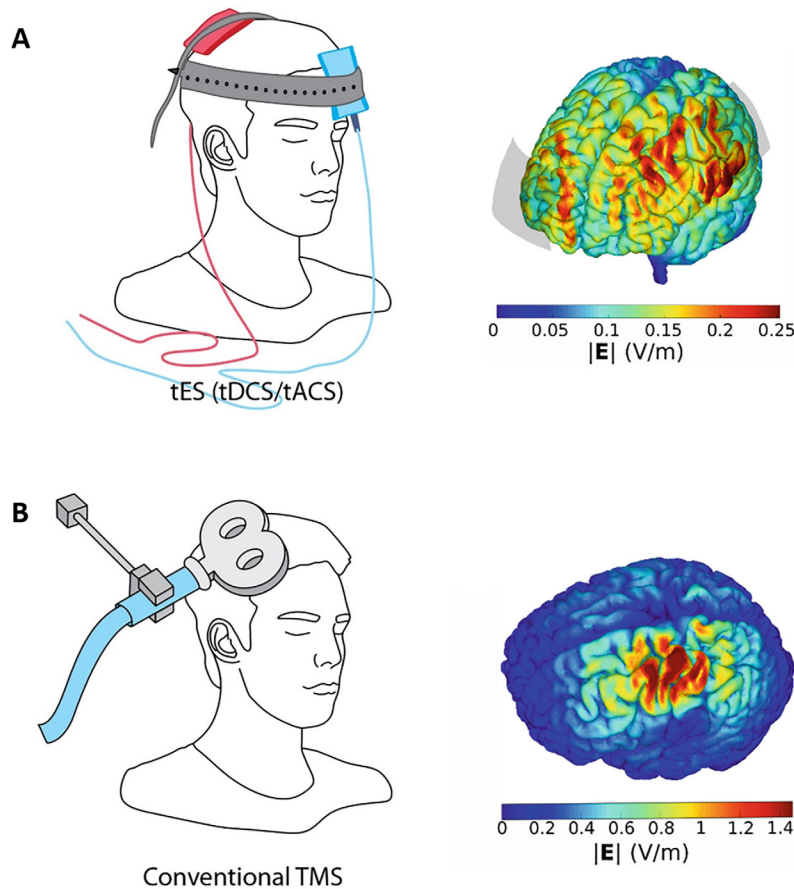


FIG. 11 Schematic representation of (A) tDCS and associated brain current modelling and (B) TMS and associated brain current modelling. tDCS is shown to be associated with a more diffuse pattern of current flow, compared to TMS which has a more focal current flow. tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; tES, transcranial electrical stimulation; V/m, volts per meter (intensity of electric field). Images adapted from Ekhtiari, H., Tavakoli, H., Addolorato, G., Baeken, C., Bonci, A., Campanella, S., ... Claus, E. (2019). Transcranial electrical and magnetic stimulation (tES and TMS) for addiction medicine: A consensus paper on the present state of the science and the road ahead. *Neuroscience and Biobehavioral Reviews*, 104, 118–140. Copyright 2019 Elsevier, and Saturnino, G. B., Puonti, O., Nielsen, J. D., Antonenko, D., Madsen, K. H., & Thielscher, A. (2019). SimNIBS 2.1: A comprehensive pipeline for individualized electric field modelling for transcranial brain stimulation. *Brain Human Body Modeling*, 3–25. Creative Commons 4.0.

Applications to other areas of neuroscience

In this chapter, we review attention and working memory related cortical activations in children and adults following traumatic brain injury (TBI). Within this topic, we address the clinical and neurophysiological changes, which occur in the acute and chronic phases of TBI and discuss possible techniques which may improve injury-related deficits.

Executive functioning in the brain depends on a variety of cognitive functions. As such, attention and working memory processes are strongly interrelated with other executive functions including cognitive flexibility, self-regulation, and task-switching. These functions are underpinned by neural networks such as the salience, executive control, and default mode networks. Understanding the mechanisms behind working memory and attention-related dysfunction provides insight into the effect of TBI on various executive functions in the brain. This is particularly important in the context of TBI, which is characterized by diffuse injury to various white matter tracts in the brain.

Traumatic brain injury is associated with various other conditions, which are associated with similar changes in cortical activation. These conditions are presented in [Table 1](#).

Finally, as discussed in the final subsection of this chapter, non-invasive brain stimulation is an evolving and emerging technique which may hold promise in improving attention and working memory-related functions in TBI populations. Understanding the mechanisms underlying non-invasive brain stimulation in TBI may provide greater insight for the application of this technique in other clinical populations.

TABLE 1 Conditions related to traumatic brain injury which impact attention and working memory-related cortical activations.

Condition	Implications for attention and working memory cortical activations
Anxiety disorders	The risk of anxiety disorders is thought to be increased following a traumatic brain injury. Individuals with anxiety disorders may have impaired attention and working memory functions, as these disorders deplete cognitive resources. This is related to abnormal cortical activation in executive areas such as the dorsolateral prefrontal cortex
Attention-deficit/hyperactivity disorder (ADHD)	Traumatic brain injury is associated with both primary and secondary ADHD. Patients with primary ADHD may have an increased risk of TBI, where the frequency of pre-existing ADHD in moderate to severe cases is between 19% and 48%. TBI is also associated with development of secondary ADHD, where adults and children with TBI have a 4–5 times greater risk of developing secondary ADHD compared to those without TBI. ADHD is associated with difficulties with attention, hyperactive behavior, and impulsiveness, which has been associated with abnormal cortical activation in the right inferior frontal cortex and dorsolateral prefrontal cortex
Depression	Increased rates of depression are one of the more frequently reported neurobehavioral sequelae following TBI. Depression is thought to affect the allocation of attention and elements of working memory. It is associated with decreased activation of the dorsolateral prefrontal cortex, striatum, medial frontal cortex, and medial temporal cortex
Learning difficulties	Traumatic brain injury may result in learning difficulties in children due to problems with executive functions such as attention and working memory. This may impact educational attainment in school. Problems with attention and working memory following TBI are related to abnormal activation of the dorsolateral prefrontal cortex and right inferior frontal gyrus
Post-traumatic stress disorder (PTSD)	Similar to anxiety disorders, the risk of post-traumatic stress disorder is thought to be increased following traumatic brain injury. Post-traumatic stress disorder can impair attention and working memory by depleting cognitive resources. This is related to abnormal cortical activation in executive areas such as the dorsolateral prefrontal cortex
Sleep disturbance	Sleep disturbance is a common symptom following traumatic brain injury. Although complex in etiology, lack of sleep is associated with poorer attention and working memory performance, which may correlate with decreases in activation of the right inferior frontal gyrus

Mini-dictionary of terms

Traumatic brain injury: Commonly abbreviated to TBI. Describes a head injury which may be caused by a blow to the head or shaking of the head and body.

Attention: An executive function in the brain which involves concentration on a certain stimulus while ignoring competing stimuli.

Response inhibition: An executive function in the brain which involves suppressing inappropriate actions in a certain context which hinder a goal-driven behavior.

Working memory: An executive function which allows temporary storage of information to guide decision-making or problem solving.

Dorsolateral prefrontal cortex: An area of the brain located in the frontal region which is important for executive functions such as attention and working memory.

Salience network: A large-scale brain network important in attention which predominantly comprises the anterior and posterior insula and dorsal anterior cingulate cortex.

Default mode network: A large-scale brain network which is active during internally focused attention, such as introspection or meditation

Functional magnetic resonance imaging: Commonly abbreviated to fMRI. A non-invasive imaging technique which is used to measure changes in blood oxygen levels during completion of a task. This is often used to help ascertain brain regions active during certain brain processes.

White matter tracts: Myelinated fibers in the brain which are responsible for conveying information across or within hemispheres, or to areas outside of the brain.

Diffuse axonal injury: An injury that commonly occurs following traumatic brain injury, involving damage to the white matter tracts of the brain due to rapid movement of the brain inside the skull.

Connectivity: This refers to a pattern of structural or functional linkage between areas of the brain. This can be studied from the neuronal to brain region level.

Key facts of working memory and attention

- Attention and working memory are the most commonly affected executive functions following a traumatic brain injury.
- Attention and working memory functions are strongly interrelated, and are controlled by the salience, central executive and default mode networks.
- Diffuse damage sustained following traumatic brain injury can cause a failure to deactivate the default mode network during cognitive tasks, which may cause deficits in working memory and attention
- Working memory has several different components, including the phonological loop, visuo-spatial sketchpad and episodic buffer
- Attention can be captured either voluntarily (i.e., when one chooses to shift their attention to a new stimulus) or involuntarily (i.e., when one's attention is captured by a salient stimulus)
- Attention and working memory undergo rapid development over the course of early childhood to late adolescence

Summary points

- Traumatic brain injury is a leading cause of morbidity and mortality worldwide, with the highest prevalence in children.
- Attention (i.e., inhibition) and working memory are the most commonly affected executive functions following a traumatic brain injury.
- These executive functions are supported by rich, interconnected neural networks such as the salience, central executive and default mode networks.
- The Stop Signal and *n*-back tasks are commonly used in both behavioral and neuroimaging settings to measure inhibition and working memory, respectively.
- From childhood to adulthood, executive networks in the brain undergo wide-scale maturational changes, characterized from diffuse to focal activation of cortical regions.
- Traumatic brain injury is a diffuse injury which causes damage to white matter tracts, disrupting structural and functional connectivity within these networks.
- The default mode network is particularly implicated in traumatic brain injury, where abnormal activation of this network is thought to underlie deficits in attention and working memory.
- Traumatic brain injury also results in other structural and functional changes, including changes in cortical thickness and connectivity within the cortico-striatal-thalamo-cortical loop.
- Non-invasive brain stimulation is an emerging technique which has been used to improve attention and working memory function following traumatic brain injury by modulating cortical activity in certain regions of the brain.

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