

**REVIEW ARTICLE****Catecholamines and cognition after traumatic brain injury****Peter O. Jenkins,<sup>1</sup> Mitul A. Mehta<sup>2</sup> and David J. Sharp<sup>1</sup>**

Cognitive problems are one of the main causes of ongoing disability after traumatic brain injury. The heterogeneity of the injuries sustained and the variability of the resulting cognitive deficits makes treating these problems difficult. Identifying the underlying pathology allows a targeted treatment approach aimed at cognitive enhancement. For example, damage to neuromodulatory neurotransmitter systems is common after traumatic brain injury and is an important cause of cognitive impairment. Here, we discuss the evidence implicating disruption of the catecholamines (dopamine and noradrenaline) and review the efficacy of catecholaminergic drugs in treating post-traumatic brain injury cognitive impairments. The response to these therapies is often variable, a likely consequence of the heterogeneous patterns of injury as well as a non-linear relationship between catecholamine levels and cognitive functions. This individual variability means that measuring the structure and function of a person's catecholaminergic systems is likely to allow more refined therapy. Advanced structural and molecular imaging techniques offer the potential to identify disruption to the catecholaminergic systems and to provide a direct measure of catecholamine levels. In addition, measures of structural and functional connectivity can be used to identify common patterns of injury and to measure the functioning of brain 'networks' that are important for normal cognitive functioning. As the catecholamine systems modulate these cognitive networks, these measures could potentially be used to stratify treatment selection and monitor response to treatment in a more sophisticated manner.

1 The Division of Brain Sciences, The Department of Medicine, Imperial College London, UK

2 Department of Neuroimaging, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

Correspondence to: Professor David Sharp,  
Computational, Cognitive and Clinical Neuroimaging Laboratory,  
3rd Floor, Burlington Danes Building, Hammersmith Hospital,  
Du Cane Road, London,  
W12 0NN, UK  
E-mail: david.sharp@imperial.ac.uk

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**Abbreviations:** DAT = dopamine transporter; DMN = default mode network; ICN = intrinsic connectivity network; NMDA = N-methyl D-aspartate; PFC = prefrontal cortex; SN/CoN = salience/cingulo-opercular network; SPECT = single photon emission computed tomography; TBI = traumatic brain injury

**Introduction**

In the developed world traumatic brain injury (TBI) is the biggest cause of death and disability in the under-40s (Bruns and Hauser, 2003). Patients can be left with significant disabilities, requiring lifelong care with high social and

economic costs. Cognitive problems, including impairments of attention, memory and executive functions, are a major cause of this ongoing disability (Whitnall *et al.*, 2006) and are difficult to treat effectively.

The heterogeneity of the injuries and the variability of the resulting cognitive problems make their management

particularly problematic. What is required are ways of identifying common underlying pathologies that can guide the use of treatment that enhances cognition. A promising approach is to consider the effects of TBI on neuromodulatory transmitter systems. Dysfunction of these systems is common after TBI and many potential therapeutic strategies are available. Dopamine (Bales *et al.*, 2009), noradrenaline (Kobori *et al.*, 2006), acetylcholine (Salmond *et al.*, 2005), and serotonin (Rosenthal *et al.*, 1998) are implicated in the pathogenesis of cognitive and neuropsychiatric symptoms following TBI. In this review we focus on the catecholamines (dopamine and noradrenaline).

The evidence implicating disruption to the catecholaminergic systems is mainly 3-fold: (i) they modulate the cognitive functions commonly impaired following TBI; (ii) disruption to these systems are seen following TBI; and (iii) catecholaminergic drugs treat some cognitive deficits seen after TBI. Despite a clear rationale for treatment, the effects of catecholaminergic medications are inconsistent (Forsyth *et al.*, 2006). This inconsistency is probably due to the heterogeneity of traumatic injuries as well as the non-linearity of the relationship between catecholaminergic levels and cognitive function (Cools and D'Esposito, 2011). This individual variability motivates a need to define the state of a person's catecholaminergic systems prior to choosing treatment.

A number of neuroimaging approaches that quantify catecholaminergic state and the response to treatment are available. Molecular imaging techniques such as single photon emission computed tomography (SPECT) and PET directly measure the catecholamine systems (Egerton *et al.*, 2009; Lehto *et al.*, 2015). Structural MRI can measure damage to catecholaminergic nuclei, their efferent projections or the areas they project to. Functional MRI can assess brain network dysfunction and response to treatment (Husain and Mehta, 2011; Sharp *et al.*, 2014). Here we give a brief review of catecholaminergic anatomy, highlighting how it might be susceptible to damage following TBI. We then review evidence that the catecholaminergic systems are disrupted after TBI, discuss the cognitive deficits commonly seen after TBI and how the catecholamines modulate them. We then highlight evidence for the use of catecholaminergic treatments and finally discuss how advanced neuroimaging techniques may be employed to direct and monitor catecholaminergic treatments effectively.

## Catecholaminergic anatomy and physiology in the context of traumatic brain injury

Dopamine and noradrenaline modulate brain function via widespread ascending projections from their small brainstem nuclei (Fig. 1) (for detailed reviews see Beaulieu and Gainetdinov, 2011; Haber, 2014; Chandler, 2015). These

nuclei, their ascending efferent pathways and their regulatory inputs are vulnerable to traumatic injury (Fig. 2).

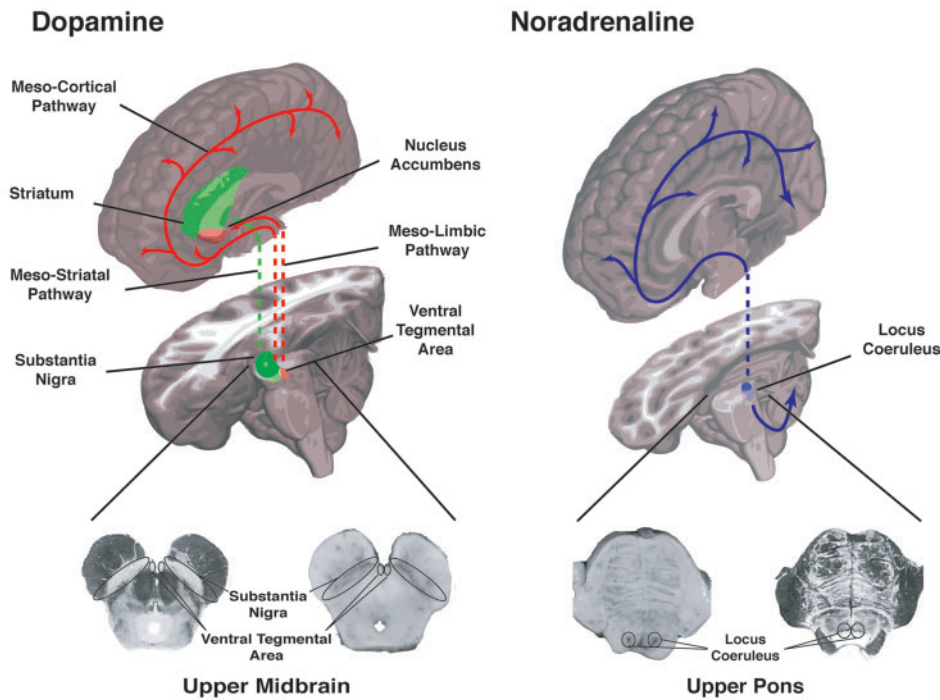
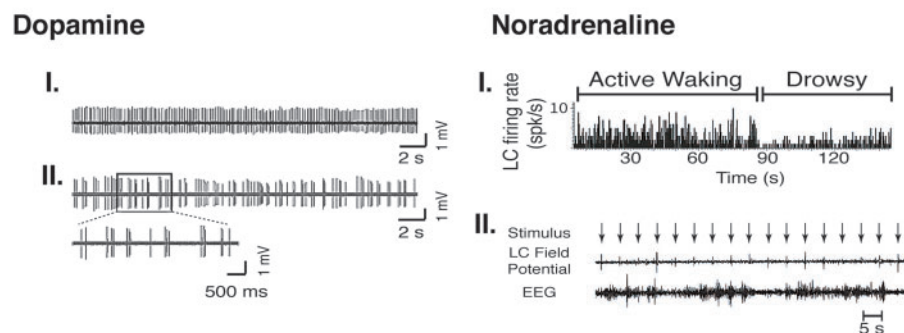
Dopaminergic projections originate from a cluster of midbrain nuclei, predominantly the substantia nigra pars compacta and the ventral tegmental area (Bjorklund and Dunnett, 2007). Noradrenergic projections to the cerebral cortex originate from the locus coeruleus in the pons (Dahlstrom and Fuxe, 1964). The catecholaminergic nuclei are therefore susceptible to brainstem injuries, which are common following TBI, particularly in patients with poor outcome (Adams *et al.*, 1989) (Fig. 2A). This susceptibility to injury may have a biomechanical explanation with computational models of TBI predicting high strain across the midbrain as a result of the brain pivoting in this region (Zhang *et al.*, 2001).

Catecholaminergic neurons may also be more susceptible to disruption due to their physiological characteristics. Dopaminergic neurons have a high baseline activity causing elevated mitochondrial stress and increased vulnerability to toxins (Lotharius *et al.*, 1999; Surmeier *et al.*, 2010a, b). This maybe important early after injury when the brain is under acute stress and may also make the cells vulnerable to persistent effects seen after TBI, such as increased neuroinflammation (Fig. 2C) (Ramlackhansingh *et al.*, 2011).

The catecholaminergic neurons project via ascending pathways to subcortical and cortical target areas. In extreme cases these axons may be severed (primary axotomy). More commonly injury is produced through a biochemical cascade leading to delayed cell death occurring over the following hours to months (secondary axotomy) (Maxwell *et al.*, 1997). Catecholaminergic axons may be particularly vulnerable to axonal injury. First, the length of their fibres and diffuse projection patterns expose them to the differential shearing stresses (Fig. 2B). Second, the huge size of their axonal arbour is associated with a high energy cost for neural transmission, making them vulnerable to metabolic stress (Pissadaki and Bolam, 2013) (Fig. 2D). Third, catecholaminergic projections are poorly myelinated or unmyelinated making them more susceptible to mechanical injury (Reeves *et al.*, 2005; Staal and Vickers, 2011).

Disruption to the afferent inputs to the catecholaminergic systems may also occur following TBI. Dopaminergic nuclei receive afferent input from the locus coeruleus and vice versa. In addition, cortical regions such as the prefrontal cortex (PFC) project into these nuclei (Arnsten and Goldman-Rakic, 1984; Sara, 2009; El Mansari *et al.*, 2010). Hence, multifocal damage either within the brainstem or in widespread cortical or subcortical locations can have a complex effect on the regulatory inputs of these neuromodulatory systems.

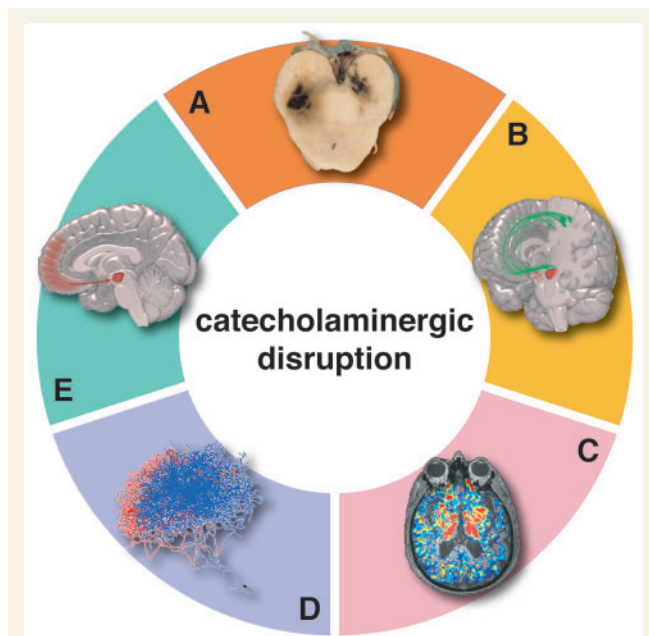
The catecholaminergic systems have complex cellular signalling mechanisms that can be disrupted following TBI (Fig. 3). Dopamine is synthesized via the hydroxylation and decarboxylation of L-tyrosine. In noradrenergic neurons, dopamine beta-hydroxylase then catalyses the synthesis of noradrenaline from dopamine (Grzanna and Molliver, 1980). Both are stored in vesicles for release at the

**A Brainstem Nuclei and Ascending Efferent Pathways****B Tonic and Phasic Firing Patterns**

**Figure 1 Anatomy and firing patterns of the catecholaminergic systems.** (A) Catecholaminergic efferent pathways and brainstem nuclei. The dopaminergic system has three main efferent projections; the meso-striatal (green), meso-limbic and meso-cortical (both in red). The meso-striatal projection supplies the striatum, the meso-limbic the limbic system including the nucleus accumbens and the meso-cortical projection supplies the majority of the cortex. The dopaminergic nuclei (the substantia nigra and ventral tegmental area) reside in the upper midbrain. The main nucleus of the noradrenergic system is the locus coeruleus and is housed in the posterior pons. The locus coeruleus provides the sole noradrenergic supply to most cortical regions. (B) Dopamine: (I) Tonic single spike activity in an inhibited dopaminergic neuron. (II) Bursting activity in a dopaminergic neuron in response to a stimulus (electric foot shocks in an anaesthetized rat). Adapted with permission from Brischoux *et al.* (2009). Noradrenaline: (I) Noradrenergic neurons in the locus coeruleus (LC) show increased firing rate depending on arousal level. Adapted from Bouret and Sara (2010). (II) Sensory evoked field potentials in the locus coeruleus vary according to the arousal state (as measured via electroencephalogram). Largest locus coeruleus field potential responses occur for stimuli experienced whilst the animal is awake as opposed to during sleep. Adapted with permission from Aston-Jones and Bloom (1981b).

presynaptic membrane. Once released, dopamine is inactivated either via reuptake through the dopamine transporter (DAT, encoded by *SLC6A3*) on dopaminergic neurons or via uptake by glial cells (Meiser *et al.*, 2013). It is then either repackaged into vesicles for reuse or enzymatically broken down by catechol-O-methyl transferase (COMT) or

monoamine oxidase. DAT is expressed exclusively on dopaminergic neurons. It is most highly concentrated in the substantia nigra, ventral tegmental area, striatum and nucleus accumbens, and more sparsely in cortical regions (Ciliax *et al.*, 1999). Dopamine reuptake via DAT is the primary mechanism controlling the lifetime of extracellular dopamine



**Figure 2 Potential mechanisms for catecholaminergic disruption following TBI.** (A) Haemorrhagic contusions in the brainstem following TBI. The high shearing stresses present in this region during trauma mean the catecholaminergic nuclei that reside in the midbrain are susceptible to damage. (B) The long, tortuous pathway of the efferent catecholaminergic axons throughout the cerebrum exposes them to shearing forces at the time of injury. (C) A  $^{11}\text{C}$ -(R)PK11195 (PK) PET image showing persistent microglial activation following TBI (Ramlackhansingh *et al.*, 2011), which may cause persisting neuronal injury. (D) Reconstruction of a single nigrostriatal dopaminergic axon showing the extensive arborization of these neurons, which may make them vulnerable to metabolic disturbances. Adapted with permission from Matsuda *et al.* (2009). (E) Damage to the PFC following TBI may disrupt the ‘top-down’ control that PFC neurons exert over the dopaminergic and noradrenergic cell bodies in the brainstem.

in areas of high DAT expression (Gainetdinov *et al.*, 1998). In addition, DAT levels are regulated by dopamine itself via interaction with the transporter and presynaptic autoreceptors (Williams and Galli, 2006). The noradrenaline transporter primarily controls the reuptake of noradrenaline. However, it also displays a high affinity for dopamine. Therefore, in areas of low DAT, such as the PFC, noradrenaline transporter plays a prominent role in dopamine clearance (Husain and Mehta, 2011). To support this, noradrenaline transporter inhibitors increase both noradrenaline and dopamine levels in the PFC without affecting striatal dopamine levels (Carboni *et al.*, 1990; Bymaster *et al.*, 2002). In addition to noradrenaline transporter, COMT also plays a role in dopamine clearance in the PFC. A common genetic variation in COMT, which alters dopamine clearance rates, results in

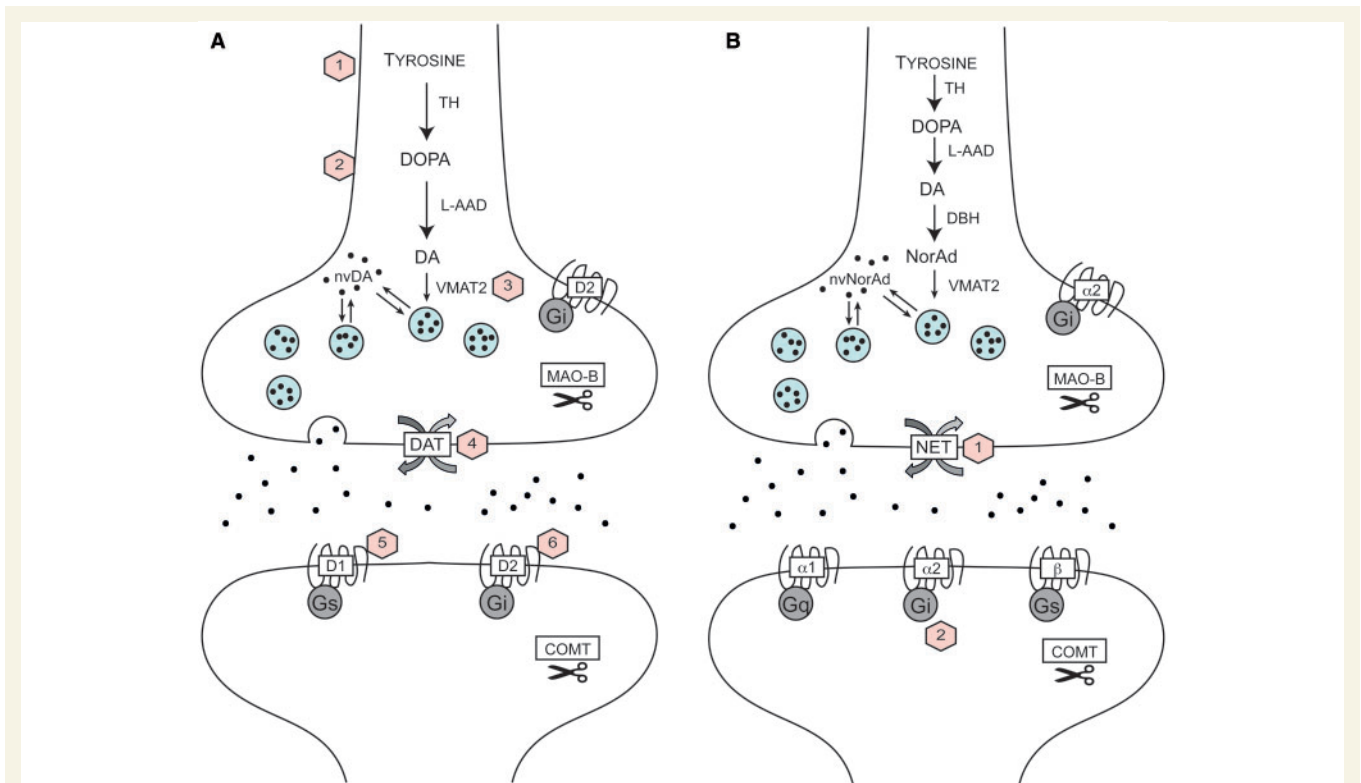
differing levels of dopamine in the PFC (Tunbridge *et al.*, 2006).

The catecholaminergic systems have multiple receptors with differing functions. Dopamine interacts with two pharmacologically and physiologically distinct receptor families, the D1-like (D1 and D5) and D2-like (D2, D3, D4). See Table 1 for a summary and Beaulieu and Gainetdinov (2011) for a detailed review. For noradrenaline, three basic receptor subtypes have been classified,  $\alpha$ -1,  $\alpha$ -2 and  $\beta$  receptors. These subtypes differ in terms of binding affinity, second messenger coupling and localization (Table 1).

Both catecholaminergic neurons display tonic and phasic discharge patterns, with distinct proposed roles (Fig. 1). This is an important issue when considering treatment, as systemic drug administration can modulate tonic levels but cannot reproduce the phasic neuromodulation. In dopaminergic neurons, phasic activity consists of a burst of neuronal discharges causing a rapid rise in intra-synaptic dopamine levels. An efficient reuptake system in the synapse means that this increase is transient and does not raise extracellular dopamine levels (Floresco *et al.*, 2003). This phasic activity has been extensively investigated and appears to code for motivational value and salience as well as acting as an alerting signal to sensory cues (Bromberg-Martin *et al.*, 2010; Chang *et al.*, 2016). In contrast, tonic activity is characterized by regular, slow, continuous discharges. The number of dopaminergic neurons firing in this pattern correlates closely with the concentration of extra-synaptic dopamine levels and has been proposed to play a more general role in preparing an organism to respond to environmental cues (Grace, 1991; Floresco *et al.*, 2003).

In noradrenergic neurons, tonic activity is related to the animal’s behavioural state. During sleep and low arousal states tonic activity is low. When the animal is awake and alert there is moderate tonic firing, rising to higher rates during unregulated stress (Foote *et al.*, 1980; Aston-Jones *et al.*, 1999). Extracellular levels of noradrenaline are linearly related to the tonic discharge rates of noradrenergic neurons (Berridge and Abercrombie, 1999). Phasic activity comprises a brief burst of two to three action potentials followed by a prolonged period of suppression. It occurs in response to behaviourally relevant stimuli and is most strongly generated during moderate tonic activity, i.e. when the animal is in an optimal state for task-focused behaviour (Foote *et al.*, 1980; Aston-Jones and Bloom, 1981*b*). However, during stress or fatigue, phasic firing becomes less discriminatory and occurs in response to distractors in addition to task-relevant stimuli (Aston-Jones *et al.*, 1999). Repeated stimulus presentation attenuates the phasic firing response with a resultant attenuation in the behavioural response. In animals, this phasic response has been closely associated with sustained attention in tests of vigilance (Aston-Jones *et al.*, 1994).





**Figure 3 Components of the catecholaminergic synapses. (A) Dopamine:** The hexagons outline potential SPECT/PET ligand targets. Example ligands are (1)  $^{18}\text{F}$ -fluoro-m-tyrosine or  $^{11}\text{C}$ -methyl-m-tyrosine; (2)  $^{18}\text{F}$ -DOPA or  $^{11}\text{C}$ -DOPA; (3)  $^{11}\text{C}$ -DTBZ; (4)  $^{123}\text{I}$ -Beta-CIT,  $^{123}\text{I}$ -FP-CIT,  $^{11}\text{C}$ -cocaine; (5)  $^{11}\text{C}$ -SCH 23390,  $^{11}\text{C}$ -NNC 112; (6)  $^{11}\text{C}$ -PHNO,  $^{11}\text{C}$ -raclopride. **(B) Noradrenaline:** (1)  $^{11}\text{C}$ -MRB; (2)  $^{11}\text{C}$ -ORM-13070. DOPA = L-3,4-dihydroxyphenylalanine; DA = dopamine; nvDA = non-vesicular dopamine; VMAT2 = vesicular monoamine transporter 2; Gs = stimulative regulative G protein (stimulates adenylyl cyclase); Gi = inhibitory regulative G protein (inhibits adenylyl cyclase); MAO-B = monoamine oxidase B; TH = tyrosine hydroxylase; L-AAD = L-amino acid decarboxylase; DBH = dopamine beta-hydroxylase; NET = noradrenaline transporter; Gq = G protein acting via phosphoinositol second messenger system; NorAd = noradrenaline; nvNorAd = non-vesicular noradrenaline.

## Evidence of catecholaminergic disruption in traumatic brain injury

### Dopamine

TBI disrupts the dopamine system in animal models. Cell loss occurs in the substantia nigra following cortical injury, with a 25% reduction in dopaminergic neurons in the substantia nigra observed after 28 days in one model (van Bregt *et al.*, 2012). The loss is progressive, rising from 15% ipsilateral to injury at 11 days to 30% bilaterally at 26 weeks (Hutson *et al.*, 2011), and is associated with blood–brain barrier breakdown and microglial activation, demonstrating an accompanying inflammatory process.

Dopamine levels have been shown to rise after TBI in numerous regions throughout the brain including the brainstem, striatum, hypothalamus and medial prefrontal cortex (Huger and Patrick, 1979; McIntosh *et al.*, 1994; Massucci *et al.*, 2004; Kobori *et al.*, 2006). However, these increases

are short-lived and followed by a hypodopaminergic functional state (Wagner *et al.*, 2005b). For example, dopamine release, clearance and evoked overflow levels of dopamine in the striatum are reduced 2 weeks after injury (Wagner *et al.*, 2005b). The reduced clearance in the context of reduced dopamine release is likely to be a compensatory mechanism aimed at maintaining extracellular dopamine levels. In addition, tyrosine hydroxylase levels are normal or raised following TBI (Wagner *et al.*, 2005b; Yan *et al.*, 2007), providing a further potential compensatory mechanism. The reduction in dopamine release in the context of normal or increased synthesizing capacity implies a deficit in vesicular trafficking, a reduction in the amount of dopamine per vesicle, and/or an alteration of the usual auto feedback control of dopamine release.

D1 and D2 receptor levels do not appear to be altered chronically in animal models of TBI (Henry *et al.*, 1997; Wagner *et al.*, 2005b, 2009a). In contrast, DAT expression is reduced (Yan *et al.*, 2002; Wagner *et al.*, 2005a, b, 2009a; Wilson *et al.*, 2005b; Shimada *et al.*, 2014). Striatal DAT expression is rapidly affected by dopamine levels, neural activity and DAT inhibitors (Daws *et al.*,

**Table 1 Dopamine and noradrenaline receptors' anatomical expression and functions**

Receptor	Expression	Function
<b>Dopamine D1-like</b>		
<b>D1</b>	Most abundant and widespread dopamine receptor. Exclusively located in postsynaptic sites on cells receiving dopaminergic innervation (Civelli <i>et al.</i> , 1991). Located in all areas receiving dopaminergic innervation, but highest expression in the PFC (Lidow <i>et al.</i> , 1991; Missale <i>et al.</i> , 1998). Located on postsynaptic dendrites in cortical regions (Zhou <i>et al.</i> , 1990) and on non-synaptic spines in the striatum (Caille <i>et al.</i> , 1996), suggesting differing roles in cortical and striatal regions. Expressed in PFC, entorhinal cortex, substantia nigra, hypothalamus and hippocampus (Beaulieu and Gainetdinov, 2011). Much lower expression than D1 but 10-times higher affinity (Missale <i>et al.</i> , 1998).	Synergistic effect with the D2 receptor in increasing locomotor activity (Missale <i>et al.</i> , 1998) Necessary for normal learning, memory, reacting to external stimuli and reward mechanisms (Tan <i>et al.</i> , 2003). Modulates the activity of D2 receptors and regulates neuron growth, differentiation, survival, long-term potentiation and synaptic plasticity (Schinelli <i>et al.</i> , 1994; Undie <i>et al.</i> , 1994; Missale <i>et al.</i> , 1998) Attenuates locomotor behaviour (Tan <i>et al.</i> , 2003).
<b>D5</b>		
<b>D2-like</b>		
<b>D2</b>	Expressed mainly in the striatum with minimal expression in other areas (Missale <i>et al.</i> , 1998). Expressed both pre- and postsynaptically (Beaulieu and Gainetdinov, 2011).	Two alternatively spliced isoforms: D2S (D2-short) and D2L (D2-long) (Usiello <i>et al.</i> , 2000). D2S is mostly expressed as a presynaptic autoreceptor, generally decreasing dopamine release and reducing locomotor activity. In contrast, D2L is a postsynaptic receptor that stimulates locomotion (Missale <i>et al.</i> , 1998; Sibley, 1999). As presynaptic autoreceptors are activated by lower concentrations than postsynaptic receptors, D2 receptor agonists can have a biphasic effect, with lower doses inhibiting locomotion and higher doses stimulating it (Beaulieu and Gainetdinov, 2011). Mediates learning, memory and reward seeking behaviours (Kellendonk <i>et al.</i> , 2006; Simpson <i>et al.</i> , 2012). Moderate inhibitory effect on locomotor activity (Vallone <i>et al.</i> , 2000). Mediates reward and motivation behaviours (Simpson <i>et al.</i> , 2014). Minimal effect on locomotion (Beaulieu <i>et al.</i> , 2015). Mediates reward-seeking behaviours (Di Ciano <i>et al.</i> , 2014).
<b>D3</b>	Limited distribution with specificity for the limbic structures (Missale <i>et al.</i> , 1998). Expressed both pre- and postsynaptically (Beaulieu and Gainetdinov, 2011).	
<b>D4</b>	Lowest levels of expression in the brain. Present in the PFC, amygdala, hippocampus and hypothalamus (Beaulieu and Gainetdinov, 2011).	

(continued)

Table 1 Continued

Receptor	Expression	Function
<b>Noradrenaline</b> $\alpha 1$ ( $\alpha 1A$ , $\alpha 1B$ , $\alpha 1D$ )	Located postsynaptically throughout the cerebral cortex, thalamus, hippocampus, striatum and ventral tegmental area In primates, concentrated in the superficial layers of the PFC (Goldman-Rakic <i>et al.</i> , 1990)	Enhances excitability on target neurons
$\alpha 2$ ( $\alpha 2A$ , $\alpha 2B$ , $\alpha 2C$ )	$\alpha 2A$ , and to a lesser extent $\alpha 2C$ , are found presynaptically. All three subtypes are found postsynaptically. In primates, concentrated in the superficial layers of the PFC (Goldman-Rakic <i>et al.</i> , 1990)	Highest affinity for noradrenaline Decrease target neuron excitability and presynaptically reduce neurotransmitter release (MacDonald <i>et al.</i> , 1997). $\alpha 2A$ in the PFC facilitates cognitive functions (Arnsten and Dudley, 2005)
( $\beta 1$ , $\beta 2$ , $\beta 3$ )	Located postsynaptically throughout the cerebrum and cerebellum In primates, densest in the intermediate layers of the PFC (Goldman-Rakic <i>et al.</i> , 1990)	Lowest affinity for noradrenaline Enhance excitability Facilitate long-term potentiation (Watabe <i>et al.</i> , 2000)

2002; Gulley and Zahniser, 2003), making the changes likely to be secondary to a loss of dopaminergic cells or a compensatory downregulation of DAT due to reduced dopamine levels. Evidence suggests the latter, as vesicular monoamine transporter (VMAT), a measure of dopamine cell density, is maintained. This is in contrast to dopamine release and clearance, which is reduced (Vander Borgh *et al.*, 1995; Kilbourn *et al.*, 1996; Wagner *et al.*, 2005b).

Surprisingly, there is relatively little work describing the effects of TBI on the dopamine system in humans. Neuropathological studies of subjects who suffered repetitive head injuries show gross and microscopic changes to the substantia nigra (see Smith *et al.*, 2013 for a comprehensive review of the pathology). Although there are no pathological studies identifying changes to this structure following a single head injury, it seems plausible that they are subject to similar pathological processes.

Two imaging studies in humans have demonstrated altered DAT and D2 receptor binding in the striatum through SPECT and PET imaging (Donnemiller *et al.*, 2000; Wagner *et al.*, 2014). Donnemiller *et al.* (2000) showed a reduction in DAT binding within the striatum of over 50% via SPECT imaging using  $^{123}\text{I}$ - $\beta$ -CIT in 10 patients who had suffered a severe TBI and were in a persistent vegetative state or had persisting akinetic-rigid features. Wagner *et al.* (2014) also demonstrated reduced DAT levels in the striatum using the PET ligand  $^{11}\text{C}$ - $\beta$ -CFT; however, they found a smaller effect size of 20–30% reduction in binding, variable injury severities were thought likely to account for this discrepancy (Wagner *et al.*, 2014).

Donnemiller *et al.* (2000) also showed reduced D2 receptor binding using the SPECT tracer  $^{123}\text{I}$ -IBZM, whereas Wagner *et al.* (2014) demonstrated higher D2 receptor binding within the ventral striatum using  $^{11}\text{C}$ -raclopride. Wagner *et al.* (2014) argued that reduced dopamine after TBI may lead to an increase in D2 receptor binding due to reduced competitive binding with endogenous dopamine and/or a compensatory upregulation of D2 receptors. In the subregion where D2 receptor binding was increased (the ventral striatum), DAT levels were not reduced. Therefore, there may be regional variation in the compensatory downregulation of DAT to maintain dopamine levels, hence causing variable dopamine levels throughout the striatum. The increased injury severity of the patients reported by Donnemiller *et al.* (2000) may also have caused greater dopaminergic cell loss leading to their findings of a reduction in both D2 receptors and DAT.

## Noradrenaline

There are fewer studies with less consistent findings for the effects of TBI on the noradrenergic system. Animal studies show inconsistent alterations in noradrenaline levels after experimental TBI (McIntosh *et al.*, 1994; Prasad *et al.*, 1994; Kobori *et al.*, 2006). Studies of

noradrenergic turnover provide the most consistent results, with an acute increase over the first 30 min observed around the site of injury (Levin *et al.*, 1995; Dunn-Meynell *et al.*, 1998) followed by a reduction throughout the brain over a subacute to chronic time scale (6 h to 8 weeks) (Dunn-Meynell *et al.*, 1994, 1998; Fujinaka *et al.*, 2003). As adrenergic agents have been shown to improve recovery and  $\alpha$ -1 receptor blockade to impede it in animal models, this reduction in noradrenergic turnover in the chronic phase may impair recovery (Boyeson and Feeney, 1990; Sutton and Feeney, 1992; Dunn-Meynell *et al.*, 1997).

Noradrenergic receptors have been less extensively studied. Early work identified an acute reduction in binding to  $\alpha$ -1 adrenoreceptors at the site of injury, progressing to a more widespread reduction in  $\alpha$ -1 adrenoreceptor binding from 24 h to 30 days throughout the brain (Prasad *et al.*, 1992; Levin *et al.*, 1994). More recently, however, increased levels of  $\alpha$ -1 adrenoreceptor (*ADRA1A*) mRNA have been detected in the medial PFC 14 days post-experimental traumatic brain injury, suggesting a possible upregulation (Kobori *et al.*, 2011).

There is minimal work investigating alterations to the noradrenergic system in humans. The locus coeruleus shows neuronal cell loss following repetitive head injury but, as with the substantia nigra, there are no pathological studies examining the noradrenergic system following a single injury (Smith *et al.*, 2013). There have been no molecular imaging studies in humans.

## The role of the catecholamines in cognitive functions commonly affected by traumatic brain injury

Patients are often left with persistent cognitive impairments after TBI that limit their recovery. Next we briefly describe the relationship between the catecholamines and these impairments. We take this approach because it reflects current clinical and neuropsychological practice. However, we acknowledge that dividing cognitive deficits into somewhat arbitrary domains such as memory and attention can be problematic and that patients often show complex patterns of cognitive impairment that are not easily subdivided in this way. Therefore, in the final part of this section we provide an example of how assessing disruption at a system's level, by measuring network function, may offer a greater mechanistic insight. TBI produces disruption to the neural networks associated with cognition and the catecholamines have also been shown to modulate these networks. Therefore, this offers a potential tool by which treatment can be targeted and response monitored.

The cognitive domains commonly affected are information processing speed, attention, memory, learning and

executive functions (Levin and Kraus, 1994; Scheid *et al.*, 2006; Draper and Ponsford, 2008). A wide range of studies show that catecholamines modulate these cognitive functions, suggesting that drug treatments could be effective after TBI. However, the relationship between catecholamine levels and specific cognitive functions is complicated. Non-linear effects are seen and different neurotransmitter systems interact with each other, producing a complex mapping between neurotransmitter levels and cognitive function (Cools and D'Esposito, 2011; Husain and Mehta, 2011). While some discrimination between processes modulated by neurotransmitter systems is possible (e.g. dopamine and reinforcement learning), interactions between systems limit the degree to which selective agents for dopamine and noradrenaline can be reliably aligned to specific deficits (Husain and Mehta, 2011).

### Information processing speed

Impairment of information processing speed is common after TBI (Draper and Ponsford, 2008). Catecholaminergic drugs can modulate processing speed and conditions that reduce these neurotransmitters, such as Parkinson's disease, also affect processing speed. For example, stimulant drugs that increase catecholamine levels, including methylphenidate and D-amphetamine, can improve speed of information processing (Halliday *et al.*, 1986, 1990). In addition, age differences in processing speeds correlate with decreases in D2 receptor density (Backman *et al.*, 2000), and reaction times are speeded with dopaminergic medications in patients with reductions in dopamine secondary to Parkinson's disease (Pullman *et al.*, 1988). Noradrenaline has also been shown to influence processing speed. For example, clonidine, an  $\alpha$ -2 adrenergic agonist that reduces noradrenaline levels when acting presynaptically, slows reaction times. In contrast, yohimbine, an  $\alpha$ -2 adrenergic antagonist that increases noradrenaline levels, improves reaction times (Halliday *et al.*, 1989).

### Attention

Attention is often impaired after TBI. Deficits include orienting (Cremona-Meteyard *et al.*, 1992), focusing (Chan, 2000; Bate *et al.*, 2001), sustaining (Ponsford and Kinsella, 1992) and dividing attention (Park *et al.*, 1999). Dopamine modulates attentional processes in a region-specific manner. In rats, reduced striatal dopamine impairs response speed (Baunez and Robbins, 1999) and reduces distractibility (Collins *et al.*, 1998; Crofts *et al.*, 2001). Conversely, reduced PFC dopamine increases distractibility and impairs sustained attention (Crofts *et al.*, 2001). Hence, these two brain systems appear to work synergistically, with increases in PFC dopamine accompanied by reciprocal decreases in the striatum and vice versa (Pycock *et al.*, 1980; Roberts *et al.*, 1994; Kolachana *et al.*, 1995; Meyer-Lindenberg *et al.*, 2005). One

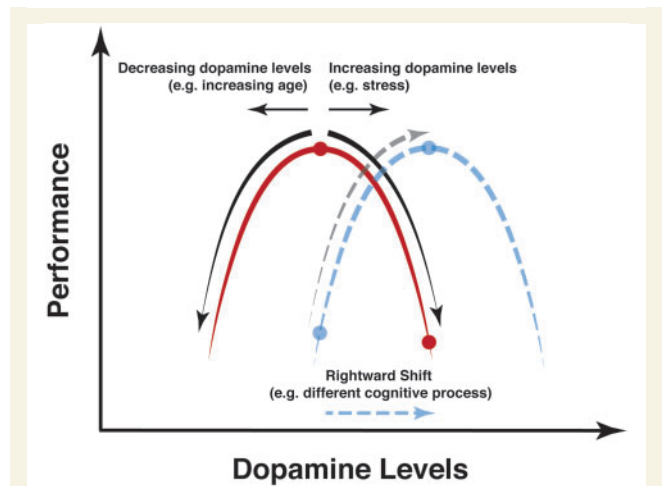


interpretation is that increased PFC dopamine stabilizes neural activity relevant to current tasks and so reduces distractibility, while increased striatal dopamine promotes shifts in attention (Cools and D'Esposito, 2011). Taken to the extreme, hypodopaminergia in the striatum would lead to perseveration whereas a similar reduction in the PFC would produce distractibility. Dopaminergic neurons are also important in signalling salient sensory cues and thereby orienting attention. Phasic release of dopamine can signal both rewarded (Schultz, 1998; Chang *et al.*, 2016) and non-rewarding experiences (Bromberg-Martin *et al.*, 2010). These dopaminergic neurons project to the dorso-lateral prefrontal cortex and dorsal striatum, and may provide an alerting signal to help orient attention to novel or important stimuli. Both increased distractibility and perseveration are seen following TBI (Mathias and Wheaton, 2007), which might reflect distinct dopaminergic abnormalities in different patients.

Noradrenaline also modulates attention, with distinct roles for tonic and phasic discharge patterns (Carli *et al.*, 1983; Cole and Robbins, 1992; Aston-Jones *et al.*, 1999). Tonic activity is related to arousal state (Foote *et al.*, 1980). Low activity levels are associated with reduced arousal and disengagement from the environment (Aston-Jones and Bloom, 1981a), moderate levels with focused task performance and appropriate filtering of irrelevant stimuli (Usher *et al.*, 1999) and high levels with distractibility and increased vigilance for irrelevant environmental events (Valentino and Van Bockstaele, 2008). In contrast, locus coeruleus neurons fire phasically in response to novel salient stimuli or to changes in the significance of a particular stimulus (Sara and Segal, 1991; Aston-Jones *et al.*, 1997; Bouret and Sara, 2004). The close relationship between the phasic activation of locus coeruleus neurons and stimulus-induced attentional shifts has led to the proposal that noradrenaline release from the locus coeruleus is also involved in controlling shifts in attention (Bouret and Sara, 2005; Yu and Dayan, 2005; Sara, 2009). In humans, pharmacological inhibition of cerebral noradrenaline release results in impaired attention (Smith and Nutt, 1996), an effect reversed by increased arousal, possibly mediated by increased noradrenaline levels. Noradrenergic drugs have also been used to enhance attentional impairment following brain injury. For example, sustained attention can be improved with the noradrenergic agonist guanfacine after non-traumatic brain injury (Malhotra *et al.*, 2006; Singh-Curry *et al.*, 2011).

## Memory and learning

Memory and learning is frequently disrupted following TBI (Draper and Ponsford, 2008). Animal studies show that memory impairments can be produced by lesioning dopaminergic neurons in animal models (Gasbarri *et al.*, 1996; Schroder *et al.*, 2003), an effect apparently caused by disruption to long-term potentiation in the hippocampus. Dopamine release in the hippocampus is required to



**Figure 4 Relationship between dopamine levels and performance.** There is an 'inverted U-shaped' relationship between dopamine levels and cognitive performance with both too little and too much dopamine causing impairment (red line). Different cognitive tasks may, however, have different optimal levels (red and blue lines representing two distinct cognitive tasks). Therefore an increase in dopamine levels (represented by blue dashed horizontal line) may impair one task (red line) while optimizing performance in another (blue line). See also Arnsten *et al.* (2012) for a molecular basis of this inverted U.

promote protein synthesis that allows cellular consolidation of these memories (Frey and Morris, 1997; O'Carroll *et al.*, 2006). In keeping with this mechanism, dopamine antagonists impair hippocampal-dependent memories after long but not short delays (Bethus *et al.*, 2010) and hippocampal activation increases hippocampal dopamine release, thereby facilitating memory encoding (Lisman *et al.*, 2011). In humans, levodopa enhances learning and memory formation in both healthy young (Knecht *et al.*, 2004) and healthy older subjects (Chowdhury *et al.*, 2012). This effect shows an inverted-U shaped dose-dependent response, with both high and low doses proving ineffective (Chowdhury *et al.*, 2012). As in animal work, the effect of dopamine is to improve delayed rather than early recollection performance.

Noradrenaline can enhance memory for emotionally arousing events, especially in the context of stress (Roosendaal *et al.*, 2009). In humans,  $\beta$  receptor antagonists block memory consolidation improvements generated via emotional arousal (Schwabe *et al.*, 2009). Noradrenergic effects on the amygdala, hippocampus and amygdala-hippocampal interactions appear to be particularly important in strengthening these emotionally salient memories (Ferry and McGaugh, 1999; Hatfield and McGaugh, 1999; Strange and Dolan, 2004; Yang and Liang, 2014). Lesions in the amygdala impair the encoding of emotionally salient events (Anderson and Phelps, 2001) and functional imaging studies show increased amygdala activity that is attenuated by  $\beta$  receptor antagonists when

subjects are presented with emotional stimuli (van Stegeren *et al.*, 2005). In addition, the noradrenergic system has been shown to modulate interactions between the amygdala and hippocampus in this context (Strange and Dolan, 2004). One interesting proposal is that the noradrenergic system may play an important role in post-traumatic stress disorder (Ramos and Arnsten, 2007). Over stimulation of the noradrenergic system may enhance the memories of stressful events via  $\alpha$ -1 and  $\beta$  receptor stimulation. To support this,  $\alpha$ -1 and  $\beta$  receptor antagonism can improve the symptoms of post-traumatic stress disorder (Peskind *et al.*, 2003; Raskind *et al.*, 2003; Vaiva *et al.*, 2003).

## Executive functions

Executive functions, such as working memory, planning, and inhibitory control, are commonly affected by TBI (Dikmen *et al.*, 1995; Stuss and Alexander, 2007; Jilka *et al.*, 2014). Dopamine has been extensively investigated with regards to its effects on executive functions, in particular working memory. Selective lesioning of the dopaminergic input to the PFC causes working memory deficits as profound as lesioning the entire PFC (Brozoski *et al.*, 1979). The D1 receptor is particularly important in mediating these effects. Administration of D1 antagonists causes selective impairments in working memory (Sawaguchi and Goldman-Rakic, 1991; Arnsten *et al.*, 1994). An ‘inverted-U’ shaped relationship between dopamine levels and working memory exists (Zahrt *et al.*, 1997), with either excessive inhibition or stimulation of PFC D1 receptors causing impaired working memory (Fig. 4). This implies the existence of an optimal level of D1 receptor activation and has fundamental implications for the effects of dopaminergic treatment on cognition (Sawaguchi and Goldman-Rakic, 1991; Williams and Goldman-Rakic, 1995; Zahrt *et al.*, 1997).

This inverted-U shaped relationship is also evident in humans. The response to dopaminergic stimulation is dependent on baseline performance level, i.e. participants with low baseline working memory capacity improve with dopaminergic medications while those with high baseline capacity are impaired (Kimberg *et al.*, 1997; Gibbs and D’Esposito, 2005). In addition, variations in the COMT gene predict performance on working memory tasks. A common functional single nucleotide polymorphism in the COMT gene results in methionine (Met) replacing valine (Val) and causes altered COMT activity. The Met allele leads to reduced COMT activity and consequently increased dopamine levels in the PFC (Cornish and Wilding, 2010). Subjects with the Met allele perform better on working memory tasks (Meyer-Lindenberg *et al.*, 2005). Furthermore, overall variation in working memory performance fits an inverted-U shaped function with those with lower and higher predicted dopamine levels performing worse (Fallon *et al.*, 2015). Low working memory is also associated with reduced dopamine synthesis capacity measured by FMT PET, which predicts the

cognitive response to administration of a dopamine agonist (Cools *et al.*, 2008, 2009).

Dopaminergic medications improve executive functions in diseases affecting dopamine levels e.g. Parkinson’s disease (Lees and Smith, 1983). Cognitive deficits are generally improved by treatment with levodopa or other dopaminergic medication (Cooper *et al.*, 1992) and are exacerbated by medication withdrawal (Lange *et al.*, 1992). However, dopaminergic medication can impair other functions. For example, following dopaminergic medication withdrawal feedback-based learning improves (Fern-Pollak *et al.*, 2004; Cools, 2006). These differential effects of treatment withdrawal, with impaired working memory and executive functions, but improved feedback-based learning, involve different striatal circuits. Working memory impairments in the hypodopaminergic state are thought to be mediated by fronto-striatal circuits passing through the dorsal striatum (Mattay *et al.*, 2002; Ekman *et al.*, 2012). The ventral portion of the striatum mediates the feedback-based learning effects (Cools *et al.*, 2007). The ventral portion of the striatum is vulnerable to ‘overdosing’ with dopamine medication as it is relatively spared of dopaminergic deficit in the early stages of Parkinson’s disease, but may be similarly vulnerable in healthy volunteers (Mehta *et al.*, 2001). Therefore, different inverted-U shaped functions may be present within different brain circuits and differentially affect different tasks mediated by these circuits (Fig. 4).

Noradrenaline modulates executive functions via its  $\alpha$ -2A receptor (Arnsten and Li, 2005). Like dopamine, animal studies show impairment of working memory with depletion of noradrenaline in the PFC (Arnsten and Goldman-Rakic, 1985). Stimulation of  $\alpha$ -2A receptors either systemically (Arnsten and Contant, 1992; O’Neill *et al.*, 2000) or locally within the PFC leads to improvements in working memory (Arnsten and Goldman-Rakic, 1985; Cai *et al.*, 1993; Mao *et al.*, 1999; Ramos *et al.*, 2006). There is some evidence that dopaminergic and noradrenergic systems improve working memory via complimentary but distinct mechanisms. For example, during a working memory task  $\alpha$ -2A stimulation increases delay period firing in the preferred direction of the neuron i.e. it strengthens the signal (Wang *et al.*, 2007), whereas D1 stimulation decreases firing in the non-preferred direction of the neuron i.e. it reduces noise (Vijayraghavan *et al.*, 2007). Noradrenaline also shows an inverted-U relationship with working memory function. However, unlike dopamine, impaired performance at higher concentrations is not caused by overstimulation of the  $\alpha$ -2A receptor (as with the D1 receptor) but rather by stimulation of the lower affinity  $\alpha$ -1 and  $\beta$  receptors (Arnsten and Jentsch, 1997; Arnsten *et al.*, 1999, 2012; Mao *et al.*, 1999).

In humans, reduced noradrenaline synthesis due to a polymorphism in the dopamine beta hydroxylase enzyme leads to impaired executive functioning and impulse control (Kieling *et al.*, 2008; Hess *et al.*, 2009) and the  $\alpha$ -2A agonist guanfacine improves working memory and planning in

healthy young adults (Jakala *et al.*, 1999), although this latter finding has not been replicated (Muller *et al.*, 2005).

## Network dysfunction and catecholamine actions

Catecholaminergic effects on the brain and treatment responses can also be described at the level of systems neuroscience. Cognitive functions frequently affected by TBI such as memory and attention depend on the coordinated action of widespread, non-adjacent brain regions (Mesulam, 1998). These distinct brain regions are connected via the white matter tracts into large-scale networks, so-called intrinsic connectivity networks (ICNs) (Seeley *et al.*, 2007). TBI commonly produces white matter damage (Strich, 1956), thereby impairing the structural connectivity between brain regions, which in turn impairs the functional interaction between network nodes and hence disrupts ICN function (Sharp *et al.*, 2014). Disruption to ICN function following TBI has been frequently demonstrated, with the degree of disruption predicting the level of cognitive impairment (Bonnelle *et al.*, 2011, 2012; Hillary *et al.*, 2011; Stevens *et al.*, 2012; Zhou *et al.*, 2012). In addition, the impact of drug treatment in other contexts on the functioning of these large-scale neural networks that underpin higher-level cognitive processes can also be informative (Husain and Mehta, 2011). Neuropsychological constructs often do not map neatly onto the functioning of these ICNs (Hampshire and Sharp, 2015). Therefore, it is likely to be informative to consider both network dysfunction after TBI and catecholaminergic treatment effects at the level of large-scale network function.

This network approach can be illustrated by considering abnormalities within specific ICNs, e.g. the default mode network (DMN) and salience/cingulo-opercular network (SN/CoN). TBI patients often show a failure to control DMN activity, with high levels of activity in the central node of the DMN (the posterior cingulate cortex) associated with slower information processing (Sharp *et al.*, 2011) and abnormalities in functional connectivity within the network associated with impaired sustained attention (Bonnelle *et al.*, 2011). These functional abnormalities are related to abnormal structural connections within the DMN (Bonnelle *et al.*, 2011) and altered interactions between the SN/CoN and the DMN (Leech and Sharp, 2014). Anti-correlated neural activity is normally observed between the DMN and a large fronto-parietal network involved in supporting task performance when attention is directed externally, the fronto-parietal control network (Kelly *et al.*, 2008). If attention is externally focused then activity within the fronto-parietal control network increases and a load-dependent decrease in DMN activity is observed (Singh and Fawcett, 2008). A loss of this tightly controlled anti-correlation is seen in a number of disease states (Leech and Sharp, 2014). After TBI this abnormal network interaction reflects abnormalities in the connections of the SN/

CoN, which appear to disrupt this network's role in switching the focus of attention in response to salient environmental events (Bonnelle *et al.*, 2012; Jilka *et al.*, 2014; Uddin, 2015).

The functioning of these networks is influenced by the catecholamines, which appear to play an important role in regulating their activity levels and interactions. Therefore, specific network abnormalities might be targeted for treatment with particular catecholaminergic drugs. The level of dopamine synthesis capacity, measured via PET imaging with the tracer 6-<sup>18</sup>F-fluoro-L-m-tyrosine, correlates positively with enhanced coupling between nodes of the SN/CoN and the DMN and reduced coupling between the SN/CoN and fronto-parietal control network at rest (Dang *et al.*, 2012). This modulation of internetwork coupling supports a role for dopamine in tuning cognitive control by regulating the interaction of these ICNs, which, as detailed above, can be impaired after TBI (Jilka *et al.*, 2014).

Pharmacological manipulation of these network interactions has also been shown with catecholaminergic medications. For example, dopamine release, induced with dextroamphetamine and measured with <sup>123</sup>I-IBZM SPECT, reduces connectivity within the DMN and SN/CoN and is positively associated with connectivity changes within a predefined cortico-striatal-thalamic network (Schrantee *et al.*, 2015). Also, levodopa administration has been shown to alter the connectivity between subcortical and cortical regions in healthy adults (Cole *et al.*, 2013b). In addition, both linear and non-linear (i.e. inverted 'U') dopaminergic effects of pharmacological manipulation on connectivity patterns have been observed with levodopa and haloperidol (Cole *et al.*, 2013a), suggesting that network responses reflect the complex relationship of catecholamines to behaviour. The cognitive enhancement produced by methylphenidate is accompanied by changes in DMN activity (Marquand *et al.*, 2011; Tomasi *et al.*, 2011). Changes in striatal dopamine have been proposed to have a key regulatory role on the functioning of the posterior cingulate cortex (Kelly *et al.*, 2009; Sambataro *et al.*, 2013) and cognitive enhancement produced by methylphenidate is accompanied by decreased activation within the posterior cingulate cortex/DMN activity (Marquand *et al.*, 2011; Tomasi *et al.*, 2011). Given the relationship between post-TBI cognitive difficulties and increased activation within the posterior cingulate cortex, this last finding provides a systems level explanation of how methylphenidate may act as a cognitive enhancer after TBI and may provide a method for predicting and measuring response to treatment.

For noradrenaline, upregulation of the noradrenergic system using clonidine (an  $\alpha$ -2 adrenoceptor agonist) in healthy human subjects performing an attentional task causes an increase in the functional connectivity on PET imaging within the fronto-parietal control network and also between the locus coeruleus and nodes of the fronto-parietal control network (Coull *et al.*, 1999). Conversely,



the administration of a noradrenergic antagonist reduces the connectivity within the SN/CoN (Hermans *et al.*, 2011). These findings imply a role for noradrenaline in modulating the neural networks involved in attentional processes and more specifically demonstrate its effects on the SN/CoN, disruption of which is associated with attentional difficulties following TBI (Bonnelle *et al.*, 2012).

## Catecholaminergic therapies

Several catecholaminergic medications have been used to treat cognitive problems following TBI with varying degrees of success. Methylphenidate and amantadine have the most evidence for efficacy (Tables 2 and 3), with less available for dextroamphetamine, bromocriptine, atomoxetine, guanfacine and levodopa (Supplementary Tables 1–5). The majority of trials have focused on using these medications as short-term cognitive enhancers, with assessment after a single dose or a short course of treatment. However, catecholamines may also have an effect on neuroplasticity, shown for example by their role in modulating hippocampal long-term potentiation (Frey and Morris, 1997; O'Carroll *et al.*, 2006; Kabitzke *et al.*, 2011; Morris and Gold, 2012). Persistent effects once treatment has finished have been less frequently studied (Kaelin *et al.*, 1996; Plenger *et al.*, 1996; Pavlovskaya *et al.*, 2007).

## Methylphenidate

### Mode of action

Methylphenidate is a psychomotor stimulant. Its primary mechanism of action is blockade of the noradrenaline and dopamine transporters (Solanto, 1998), but it also increases dopamine release via D2 receptor-dependent modulation of vesicular trafficking (Volz *et al.*, 2007, 2008). These mechanisms increase extracellular levels of both noradrenaline and dopamine, which is believed to be the primary mechanism by which methylphenidate improves cognition (Berridge *et al.*, 2006). In animal models of TBI, methylphenidate improves working memory and attention via stimulation of both D1 dopamine receptors and  $\alpha$ -2 adrenoceptors in the PFC (Arnsten and Dudley, 2005).

There is also evidence that methylphenidate might increase neuroplasticity and so promote longer-term cognitive improvements. In animal models, single doses of methylphenidate do not augment either basal or evoked extracellular dopamine levels (Wagner *et al.*, 2009b). However, 2 weeks of daily pretreatment leads to increased dopamine levels in response to the drug, implying that methylphenidate may be inducing functional changes in DAT or changes in DAT trafficking. Methylphenidate has also been shown to amplify long-term potentiation in the hippocampus (Rozas *et al.*, 2015), an effect modulated via activation of  $\beta$  adrenergic and D1/D5 receptors.

### Evidence of use

In humans, 17 studies to date have assessed methylphenidate's effect on cognition following TBI (Table 2). These studies differ greatly in design, time after injury and contain relatively few patients (range 1–44, mean 20). The majority assess the response to methylphenidate over 1–6 weeks with two studies assessing response after a single dose (Kim *et al.*, 2006, 2012). Three trials assessed whether a residual effect remained after stopping the medication (Kaelin *et al.*, 1996; Plenger *et al.*, 1996; Pavlovskaya *et al.*, 2007). In these studies, cognitive testing was repeated at 1, 3, or 8 weeks following treatment cessation, with persisting improvements seen in the studies reassessing at 1 and 3 weeks (Kaelin *et al.*, 1996; Pavlovskaya *et al.*, 2007) but not in the study that reassessed at 8 weeks (Plenger *et al.*, 1996).

The majority of trials ( $n = 9$ ) show improvements in information processing speed (Evans *et al.*, 1987; Kaelin *et al.*, 1996; Whyte *et al.*, 1997, 2004; Al-Adawi *et al.*, 2005; Kim *et al.*, 2006, 2012; Willmott and Ponsford, 2009; Willmott *et al.*, 2013; Johansson *et al.*, 2015) with one trial showing persisting improvement a week after drug cessation (Kaelin *et al.*, 1996). These improvements in speed did not come at the expense of accuracy (Whyte *et al.*, 2004; Willmott and Ponsford, 2009; Kim *et al.*, 2012).

The effect of methylphenidate on attention is less clear. One detailed trial evaluated the effect of methylphenidate on a range of attentional measures including standard cognitive tests, observed attentiveness, productivity and caregiver assessments (Whyte *et al.*, 2004). Participants were noted to be more attentive whilst performing tasks and caregiver ratings of attention were also significantly raised on treatment, suggesting functionally significant real-world benefits. Several other trials also show an improvement in attention (Evans *et al.*, 1987; Gualtieri and Evans, 1988; Plenger *et al.*, 1996; Al-Adawi *et al.*, 2005; Lee *et al.*, 2005; Kim *et al.*, 2006, 2012; Pavlovskaya *et al.*, 2007) but almost an equal number of studies failed to find a benefit (Mooney and Haas, 1993; Speech *et al.*, 1993; Whyte *et al.*, 1997; Tiberti *et al.*, 1998; Willmott and Ponsford, 2009).

There is limited evidence that methylphenidate improves memory functions. Three trials demonstrated improvements in some memory tests (Evans *et al.*, 1987; Gualtieri and Evans, 1988; Kaelin *et al.*, 1996), but the majority of trials failed to show a significant improvement (Mooney and Haas, 1993; Speech *et al.*, 1993; Plenger *et al.*, 1996; Tiberti *et al.*, 1998; Willmott and Ponsford, 2009; Kim *et al.*, 2012). Executive functions, including working memory, also fail to show a consistent improvement across studies. Two studies showed a benefit in certain executive functions, with one showing persistent benefit 1 week later (Kaelin *et al.*, 1996; Kim *et al.*, 2006). Other studies have failed to show improvements in working memory (Willmott and Ponsford, 2009; Kim *et al.*, 2012).



Table 2 Effect of methylphenidate on cognitive outcomes in TBI

Clinical studies	n	Dose of methylphenidate	Evidence class/study design	Severity of TBI	Time since TBI	Cognitive outcomes measured	Conclusion
Evans <i>et al.</i> , 1987	1	0.15 to 0.3 mg/kg twice daily	III: Double-blind, controlled crossover case study	Severe	2 years	Attention, memory, speed of information processing	Trend for improvement in sustained attention, memory and speed of information processing Trend for improvement in attention and memory
Gualtieri and Evans, 1988	15	0.15 to 0.3 mg/kg twice daily	II: Double-blind, randomized, controlled cross-over study	Severe TBI. Persistent cognitive deficit Severe	> 5 months	Attention, memory	No significant effects
Mooney and Haas, 1993	38	30 mg/day (6 week trial)	III: Single-blind, randomized, controlled study	Severe	> 6 months	Attention, memory, anger	No significant effects
Speech <i>et al.</i> , 1993	12	0.3 mg/kg twice daily	II: Double-blind, randomized, controlled cross-over study	Moderate to severe	> 1 year	Attention, learning, speed of information processing	No significant effects
Kaelin <i>et al.</i> , 1996	10	30 mg/day (1 week)	III: Observational study	Mixed	4–71 days	Attention, memory, DRS, speed of information processing	Significant improvement in speed of information processing, some memory and executive tasks and trend for improvement on functional outcome scores (DRS). Effect remained 1 week after cessation of drug.
Plenger <i>et al.</i> , 1996	23	0.3 mg/kg twice daily (1 month)	II: Double-blind, randomized, controlled parallel design	Moderate to severe	< 1 year	Attention, memory, vigilance, DRS	Improvement in functional outcome and attention after 1 month of treatment. No significant difference at 90 days.
Whyte <i>et al.</i> , 1997	19	0.25 mg/kg twice daily (6 days)	I: Double-blind, randomized, controlled, repeated crossover study	Severe	1 month–9 years	Attention, speed of information processing	Significant improvement in speed of information processing
Tiberti <i>et al.</i> , 1998	10	10–40 mg daily (6 weeks)	III: Double-blind, randomized controlled cross-over study	Ongoing amnesic disorder	> 6 months	Attention, memory, behaviour, speed of information processing	No significant effects
Whyte <i>et al.</i> , 2004	34	0.3 mg/kg twice daily (6 weeks)	I: Double-blind, randomized, controlled, repeated crossover study	Moderate to severe	4 months–34 years	Attention, speed of information processing	Significant improvement in speed of information processing, attention and caregiver ratings of attention
Al-Adawi <i>et al.</i> , 2005	12	5 to 10 mg twice daily (2 weeks)	III: Observational study	Mild to moderate	1–6 months	Attention, speed of information processing	Improvement in speed of information processing and attention.
Lee <i>et al.</i> , 2005	10	20 mg daily (4 weeks)	II: Double-blind, randomized, controlled parallel design	Mild to Moderate	2 weeks–1 year	Attention, memory	Improvement in cognitive function and alertness
Kim <i>et al.</i> , 2006	18	20 mg (single dose)	II: Double-blind, randomized controlled cross-over study	Mixed. Persistent cognitive deficit	> 6 months	Working memory, visuospatial attention, speed of information processing	Improvement in working memory, visuospatial attention and speed of information processing
Pavlovskaya <i>et al.</i> , 2007	6	5–10 mg daily (4 weeks)	III: Observational study	Severe	> 1 year	Attentional shifting	Significant improvement in attentional shifting. Effect persisted for 2–3 weeks following drug cessation.

(continued)

Table 2 Continued

Clinical studies	n	Dose of methylphenidate	Evidence class/study design	Severity of TBI	Time since TBI	Cognitive outcomes measured	Conclusion
Willmott and Ponsford, 2009	40	0.3 mg/kg twice daily (2 weeks)	I: Double-blind, randomized, controlled, repeated crossover study	Severe	12–462 days	Attention, working memory, speed of information processing	Improvement in speed of information processing
Kim <i>et al.</i> , 2012	18	0.3 mg/kg (single dose)	II: Double-blind, randomized controlled cross-over study	Moderate to severe	> 3 months	Sustained attention, working memory, speed of information processing	Improvement in sustained attention and speed of information processing
Willmott <i>et al.</i> , 2013	32	0.3 mg/kg twice daily (2 weeks)	I: Double-blind, randomized controlled cross-over study	Moderate to severe	Mean 68 days (80% < 3 months)	Attention, speed of information processing	Improvement in speed of information processing. No difference between COMT genotypes in response to methylphenidate.
Johansson <i>et al.</i> , 2015	44	Three 4-week periods: no treatment; 15 mg daily (low dose); 60 mg daily (high dose)	III: randomized, observational study	Mild to moderate	> 6 months	Speed of information processing and fatigue	Improvements in speed of information processing and fatigue scores. High dose producing greatest effect.

DRS = disability rating scale.

Two studies assessed impact on functional outcomes. A randomized, controlled study (Plenger *et al.*, 1996) showed a significant improvement in functional outcome after 4 weeks of treatment but this effect was no longer apparent 2 months after stopping medication. These results imply methylphenidate may accelerate the recovery process but its effect on longer-term outcomes is unclear.

## Amantadine

### Mode of action

Amantadine has a mixed set of actions including weak antagonism at the *N*-methyl D-aspartate (NMDA) receptor. NMDA receptors are distributed throughout the striatum with a presence on presynaptic dopamine terminals and GABA interneurons. Blockade of the former causes reductions in dopamine release and thus the latter mechanism is more likely to be important for the actions of amantadine on dopamine release. The GABAergic interneurons are located postsynaptically to the dopamine terminals in the striatum. Glutamate signalling through the NMDA receptors inhibits dopamine release via local regulation and through modulation of inputs from the ventral pallidum and cortical inputs (Kegeles *et al.*, 2000; Hernandez *et al.*, 2003). Excitatory cortical inputs into the striatum can also disinhibit striatal GABAergic interneurons (Farber *et al.*, 2003; Homayoun and Moghaddam, 2007), and this may contribute to the enhancing effects of amantadine on dopamine release.

### Evidence of use

Six studies of mixed design suggest potential improvement of cognitive problems post TBI with amantadine (Table 3). The largest study randomized 184 vegetative or minimally conscious TBI patients into either an amantadine or placebo group 4–16 weeks after injury (Giacino *et al.*, 2012). This study showed accelerated recovery in behaviour over the 4 weeks of treatment, although this effect was lost 2 weeks after drug cessation. It is therefore not clear from this study whether amantadine improves long-term outcome or accelerates the recovery process to a similar end-point. An earlier smaller study also showed accelerated recovery in the acute setting (Meythaler *et al.*, 2002). One case series, one case study and a retrospective chart review all showed improvements in measures of attention, information processing speed and executive functions when amantadine was given in the chronic phase (Nickels *et al.*, 1994; Kraus and Maki, 1997a,b). The case study showed an additional benefit when levodopa was given in combination with amantadine (Kraus and Maki, 1997a). However, another small ( $n = 10$ ) double-blind, randomized, controlled trial failed to show any significant effects (Schneider *et al.*, 1999). An interesting open-label designed study showed improvements in executive functions that correlated with increased left PFC resting metabolism identified by  $^{18}\text{F}$ -FDG PET (Kraus *et al.*, 2005),

**Table 3** Effect of amantadine on cognitive outcomes in TBI

Clinical studies	n	Dose of Amantadine	Evidence class/study design	Severity of TBI	Time since TBI	Cognitive outcomes measured	Conclusion
Nickels <i>et al.</i> , 1994	9	50–200 mg/day	III: Retrospective chart review	Moderate to severe	2–9 months	Arousal, attention, memory, and speed of information processing	8/9 improved in sustained attention, speed of information processing and alertness
Kraus and Maki, 1997b	5	Up to 400 mg/day (several weeks)	III: Observational study (case series)	Severe. Persistent cognitive deficit	> 1 year	Attention, memory, speed of information processing and executive functions	Trend towards improvement in attention and executive functions
Schneider <i>et al.</i> , 1999	10	100–300 mg/day (2 weeks)	II: Double-blind, randomized, controlled cross-over study	Moderate to severe. Persistent cognitive deficit	Unspecified	Attention, memory, executive functions and behaviour	No significant effects
Meythaler <i>et al.</i> , 2002	35	200 mg/day (6 weeks)	I: Double-blind, randomized, controlled, crossover study	Severe	2–6 weeks	General cognitive and functional outcome scores	Trend towards faster cognitive and functional recovery
Kraus <i>et al.</i> , 2005	22	400 mg/day (12 weeks)	III: Open-label	Mixed. Persistent cognitive deficit	> 6 months	Attention, memory and executive functions	Significant improvement in executive functions.
Giaco <i>et al.</i> , 2012	184	200–400 mg/day (4 weeks)	I: Double-blind, randomized, controlled study	Severe	1–4 months	Functional outcome scores	Significant improvement in speed of functional recovery

providing a possible mechanistic insight into the drug's mode of action.

## Dextroamphetamine

### Mode of action

Dextroamphetamine increases catecholamine levels by inhibiting presynaptic reuptake via downregulation of catecholaminergic transporter expression (Kahlig and Galli, 2003), stimulating catecholaminergic release and inhibiting monoamine oxidase (Fleckenstein *et al.*, 2007).

### Evidence of use

Two single case controlled studies and one retrospective observational study have assessed the use of dextroamphetamine post-TBI (Supplementary Table 1). The retrospective study identified 9 of 15 patients who responded to treatment but significant experimental flaws make interpretation of this result difficult (Hornstein *et al.*, 1996). Two studies used a double-blind, crossover design in a single patient. Both demonstrated improvements in information processing speed and sustained attention, with one also showing improvements in verbal learning (Evans *et al.*, 1987; Bleiberg *et al.*, 1993).

## Bromocriptine

### Mode of action

Bromocriptine is a selective D2 dopamine receptor agonist, binding to both presynaptic autoreceptors (which inhibit dopamine release) as well as postsynaptic sites (Fuxe *et al.*, 1981). Due to its higher affinity for the presynaptic autoreceptor, it has been proposed to have an inhibitory effect on dopamine function at lower doses, whereas at higher doses its effects at the postsynaptic receptor are thought to predominate, resulting in a facilitatory effect on the dopaminergic system (Meltzer *et al.*, 1983; Luciana and Collins, 1997).

However, one study suggested that low doses in rodents (2.5 and 5 mg/kg) could increase extracellular dopamine levels (Brannan *et al.*, 1993), aligning with *in vitro* evidence that at low concentrations bromocriptine can act as a partial D2 antagonist (Lieberman and Goldstein, 1985). The relevance of this potential increase in dopamine levels after single, low doses to the use of the drug in clinical settings is not currently known. Therefore, bromocriptine has a complex effect on the dopaminergic system that is dependent on the dose, mediated through a combination of pre- and postsynaptic effects.

### Evidence of use

There is mixed data regarding the use of bromocriptine (Supplementary Table 2). One case series identified an improvement in all cognitive outcomes measured (working memory, list learning and verbal fluency), an

effect that persisted for 2 weeks following drug cessation (Powell *et al.*, 1996). A further randomized, controlled trial showed a single low dose (2.5 mg) improved certain executive functions (e.g. planning and inhibition). Other cognitive functions such as working memory did not improve, leading the authors to conclude that bromocriptine had a targeted effect on these cognitive processes rather than a non-specific improvement in arousal or attention (McDowell *et al.*, 1998). A retrospective case review also showed a greater degree of functional recovery when used in severe cases over a 2–6 month window (Passler and Riggs, 2001). More recent randomized trials, however, using both regular higher dosing (5 mg twice daily for 6 weeks) and a single low dose (1.25 mg) failed to show a benefit in attention or working memory (Whyte *et al.*, 2008; McAllister *et al.*, 2011a).

## Atomoxetine

### Mode of action

Atomoxetine increases extracellular levels of noradrenaline via inhibition of noradrenaline reuptake. It has high affinity for the noradrenaline transporter and much lower affinity for DAT (Bymaster *et al.*, 2002). Animal models, however, have shown that in the PFC it increases dopamine levels as well as noradrenaline (Bymaster *et al.*, 2002; Swanson *et al.*, 2006), which is likely to be due to the role of the noradrenaline transporter in regulating dopamine levels in the PFC (Bari and Aston-Jones, 2013). There is also evidence that atomoxetine acts as an NMDA antagonist at clinically relevant doses (Ludolph *et al.*, 2010).

### Evidence of use

Just one trial has explored the use of atomoxetine. Fifty-one patients with a moderate-to-severe traumatic brain injury and self-reported attentional problems did not show improvement over a 2-week treatment period (Ripley *et al.*, 2014).

## Guanfacine

### Mode of action

Guanfacine is a selective  $\alpha$ -2A noradrenergic agonist. Alpha-2A receptors are predominantly concentrated in the PFC and the locus coeruleus and have been widely implicated in the control of PFC cognitive functions (Arnsten, 1998).

### Evidence of use

One trial including functional MRI showed a benefit in working memory in 13 patients with mild traumatic brain injury 1-month post-injury (McAllister *et al.*, 2011b). The functional imaging showed increased activation in working memory associated regions, suggesting its effects maybe via direct manipulation of PFC functioning. Interestingly, this group tested the same working memory paradigm with

bromocriptine and found no benefit (McAllister *et al.*, 2011a). Therefore, given the evidence that both methylphenidate (a dual dopaminergic and noradrenergic agonist) and guanfacine (a selective  $\alpha$ -2A noradrenergic agonist) improve working memory but bromocriptine (a dopamine D2 receptor agonist) does not, the results suggest that noradrenergic  $\alpha$ -2A receptor stimulation, or stimulation of dopamine D1 receptors as these can have similar downstream intracellular effects (Arnsten *et al.*, 2012), maybe key to improving working memory function.

## Levodopa

### Mode of action

Levodopa is the precursor to dopamine. It is converted within dopaminergic neurons to dopamine via the enzyme L-amino acid decarboxylase (L-AAD).

### Evidence of use

There has been one small observational study (Lal *et al.*, 1988). Twelve moderate-to-severe patients were assessed on a titrated dose of levodopa (combined with carbidopa) without placebo control. The study suggested improvements based on clinical observation in a range of cognitive domains but a formal, properly controlled study is clearly required.

## Stratifying patient treatment based on catecholaminergic function

Although there is a broad evidence base that catecholaminergic medications can improve certain cognitive impairments following TBI, the magnitude of effects in individual patients are very variable. This variability reflects the heterogeneous nature of TBI and has important implications for future work. Clinical trials in unselected TBI patients need large numbers to be adequately powered, and to date many have been underpowered (Warden *et al.*, 2006). One way to improve the design of future trials is to select patient subgroups based on the presence of specific types of neuropathology that are more likely to respond to specific cognitive enhancers. An individual's 'catecholaminergic status' is likely to be a key factor determining catecholaminergic treatment response because the synaptic concentrations of catecholamines are non-linearly related to cognitive function (the inverted-U relationship discussed above). A principled way to select patients for trials would be to define an individual's catecholaminergic state after TBI. Advanced imaging techniques using structural, molecular and functional imaging techniques all offer the potential to directly assess the catecholaminergic systems and therefore help guide treatment selection (Fig. 5). In addition, innate factors such as age, gender and genetics that alter an individual's catecholaminergic status might be



incorporated into these decisions as they influence a patients 'position' on the inverted-U curve.

## Structural imaging

Structural imaging techniques allow damage to the catecholaminergic systems to be assessed. Damage to the brainstem nuclei can be assessed visually using standard MRI sequences. For example, susceptibility weighted imaging provides a sensitive marker for microhaemorrhages. More sophisticated quantitative approaches provide additional information. Volumetric measures can quantify atrophy within brainstem nuclei [Fig. 5A(III)]. In addition, damage to the structural connections can be measured using diffusion imaging. Although the catecholaminergic fibres are poorly myelinated and therefore unlikely to be directly measured by techniques such as diffusion tensor imaging (DTI), the white matter tracts through which they travel could be used as a surrogate marker for damage to the ascending catecholaminergic fibres. In Parkinson's disease, DTI techniques have been used to assess the integrity of the 'nigrostriatal tract' and show abnormalities consistent with the degree of motor deficits in these patients (Zhang *et al.*, 2015). A similar approach could be used in TBI patients [Fig. 5A(II)], with the resulting measures potentially used as the basis for machine learning methods to predict effects of TBI in individuals (Hellyer *et al.*, 2013).

## Molecular imaging

Molecular imaging allows direct measurement of catecholaminergic function. Numerous PET and SPECT ligands are available to measure dopamine function and others are in development for the noradrenergic system (Ding, 2014; Fig. 3). The dopaminergic ligands available can be used to assess synthesis capacity, receptor density as well as dynamic endogenous release of dopamine (Farde *et al.*, 1987; Volkow *et al.*, 1994; Cumming *et al.*, 1997). These have been applied widely in Parkinson's disease and other neurodegenerative conditions (Tai and Pavese, 2013), but have been used surprisingly little in TBI.

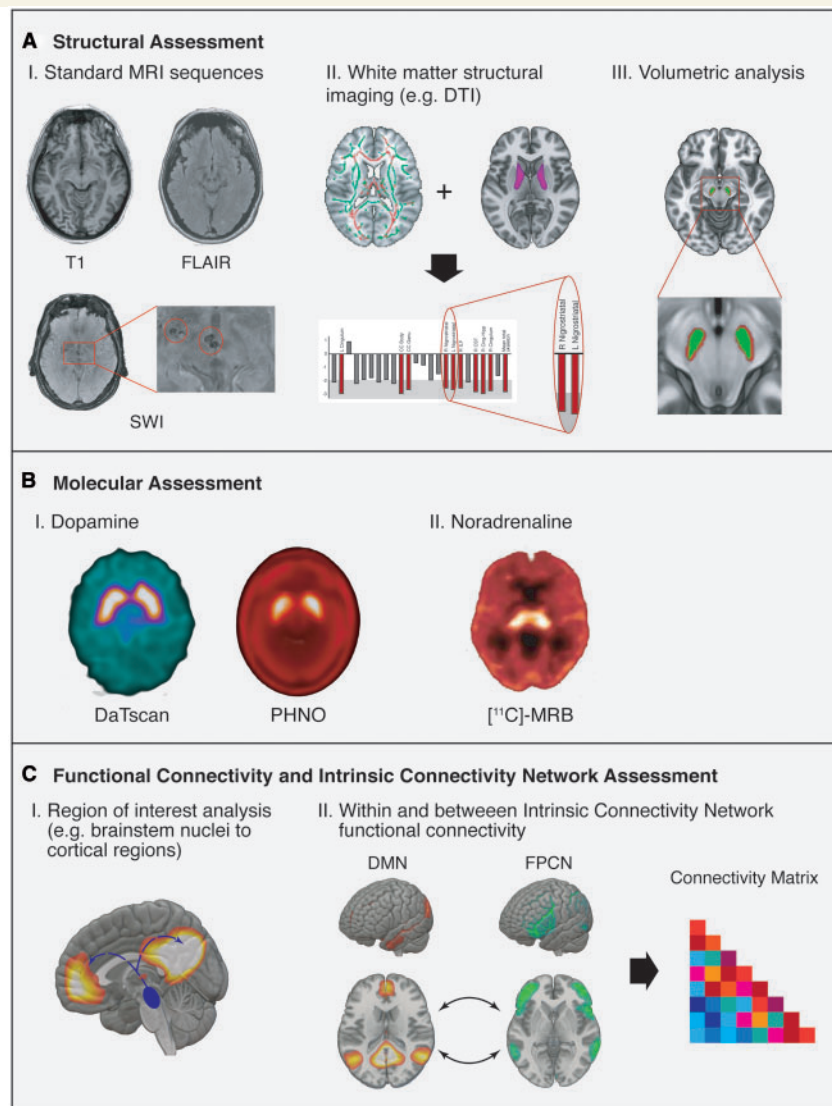
As already discussed, two studies show dopaminergic abnormalities following TBI, including reductions in striatal DAT levels using both SPECT (Donnemiller *et al.*, 2000) and PET (Wagner *et al.*, 2014). SPECT imaging offers the advantages of lower cost and commercial availability, with ligands such as  $^{123}\text{I}$ -ioflupane (DaTScan) already widely used clinically to aid the diagnosis of parkinsonian disorders. PET, however, provides greater spatial resolution and improved quantitative assessment. One important consideration to bear in mind when performing molecular imaging is the effect of atrophy or focal tissue loss, which are both common following TBI, this reduces apparent ligand binding potential and therefore needs to be accounted for when using these techniques.

In both normal ageing and Parkinson's disease, reduced striatal DAT levels have been shown to relate to cognitive deficits (Marie *et al.*, 1999; Muller *et al.*, 2000; Mozley *et al.*, 2001). However, it is currently unclear how striatal DAT levels relate to cognitive function after TBI and whether they predict treatment response. Two of the authors (P.O.J. and D.J.S.) are currently conducting a clinical trial of methylphenidate where we will test whether striatal DAT levels predict treatment response (Imperial College London, 2016).

Further molecular imaging studies are needed to explore the exact nature of catecholamine disruption in TBI patients and its relation to cognitive function.  $^{18}\text{F}$ -DOPA can be used to assess dopamine synthesis in the presynaptic terminal (Cumming *et al.*, 1997). In Parkinson's disease, reductions in this tracer in the caudate correlate with impairments in neuropsychological performance (Bruck *et al.*, 2001). Behavioural abnormalities after TBI may be mediated through distinct catecholaminergic receptors and these could be probed using molecular imaging. D1 receptors are related to many aspects of cognitive function affected by TBI and their levels can be measured using  $^{11}\text{C}$ -SCH 23390 and  $^{11}\text{C}$ -NNC 112 (Elsinga *et al.*, 2006). In addition, extrastriatal D2/3 receptors can be measured with  $^{11}\text{C}$ -PHNO, which may have relevance in neuropsychiatric problems following TBI (Wilson *et al.*, 2005a).

Animal work demonstrates a dynamic element to dopamine abnormalities after TBI, with reduced dopamine release from intact dopaminergic terminals (Wagner *et al.*, 2005). This finding suggests that dynamic measures of catecholamine function may be necessary to fully characterize abnormalities after TBI. PET provides methods to study this. For example,  $^{11}\text{C}$ -raclopride is a displaceable D2/3 receptor antagonist (Farde *et al.*, 1986) that can provide quantitative information about striatal D2/3 receptor levels, but is also sensitive to fluctuations in endogenous dopamine release as increasing dopamine levels reduce  $^{11}\text{C}$ -raclopride binding due to competitive binding (Breier *et al.*, 1997; Laruelle, 2000). This latter property allows 'dynamic' assessment of an individual's dopaminergic system in response to either medication (such as a stimulant) or increased cognitive demands (Egerton *et al.*, 2009).

The noradrenergic system has been less extensively investigated via nuclear imaging methods, although several noradrenaline transporter (NET) ligands have been developed and are increasingly being used in research (Ding, 2014). More recently, an  $\alpha$ -2C adrenoreceptor ligand ( $^{11}\text{C}$ -ORM-13070) has been shown to be sensitive to monitoring extracellular noradrenaline concentrations, thereby offering the potential to assess noradrenergic neurotransmission *in vivo* (Lehto *et al.*, 2015). As noradrenaline abnormalities are likely to be central to some cognitive impairments after TBI, the application of specific noradrenergic ligands in TBI is a promising research direction.



**Figure 5 Assessment of the catecholaminergic systems. (A)** Structural assessment. (I) Standard MRI sequences can be used to assess evidence of damage to catecholaminergic structures (e.g. the brainstem nuclei). Susceptibility weighted imaging (SWI), T<sub>1</sub> and fluid-attenuated inversion recovery (FLAIR) sequences are differentially sensitive. This example shows these three sequences in the same individual with no obvious damage on T<sub>1</sub> or FLAIR but evidence of small haemorrhages in the upper mid-brain/cerebral peduncles on susceptibility weighted imaging. (II) White matter damage is common after TBI and can be assessed using MRI techniques such as DTI. Whole brain analysis can be performed in an individual with the *top left* image demonstrating areas with increased damage (red) compared to a normative control group. By specifying a region of interest (e.g. white matter area containing the nigrostriatal tract highlighted in purple in the *top right* image), damage to specific tracts can be assessed. (III) Volumetric analysis of the substantia nigra. **(B)** Molecular assessment. (I) <sup>123</sup>I-loflupane (DaTscan) and PHNO. (II) <sup>11</sup>C-(S,S)-methylreboxetine (<sup>11</sup>C-MRB) ligand that binds to the noradrenaline transporter (Smith *et al.*, 2015). **(C)** Functional connectivity and ICN assessment. (I) Functional connectivity analyses can be used to assess impairments in functional connectivity between different regions of interest. This may provide a biomarker for damage to the catecholaminergic systems, e.g. disruption in the functional connectivity between the brainstem (blue) and cortical regions (nodes in the default mode network in red/yellow). (II) Connectivity within and between ICNs for an individual can provide a unique signature that may provide information regarding injury and relate to the cognitive deficits. Assessment of a derived connectivity matrix has the potential to be used to guide treatment as well as assessing an individual's response to treatment. FPCN = fronto-parietal control network.

## Network function

As discussed above, measuring activity within ICNs such as the DMN provides another potential method of guiding

treatment choices. Network abnormalities after TBI can be identified using techniques such as functional MRI, which could allow a more rational choice about drug treatment as information accumulates about the network effects

of particular drugs. For example, if methylphenidate is known to enhance the normal task-dependent deactivation of the DMN that is lost after TBI, then the drug would be a logical choice in patients with this network abnormality. Therefore, assessing an individual's impairments in network activity using functional MRI offers a potential mechanism by which treatment may be selected if the effect of the treatment at this network level is known (Fig. 5C) (Leech and Sharp, 2014). In addition, this approach allows treatment response to be measured. This network-based approach could be particularly useful following TBI, where patients have a wide-range of underlying causes for cognitive problems that will require distinct approaches to treatment.

### Innate and genetic factors affecting catecholaminergic status

Many innate factors also affect the catecholaminergic systems and are likely to influence the choice of treatment following TBI. Ageing reduces both dopaminergic (Kaasinen and Rinne, 2002) and noradrenergic levels (Mann *et al.*, 1980; Marcyniuk *et al.*, 1986), and influences the response to catecholaminergic drugs (Turner *et al.*, 2003; Castner and Goldman-Rakic, 2004; Sambataro *et al.*, 2012). Therefore, TBI patients would be expected to show significant age-dependent variations in treatment response. There is also evidence that gender alters the dopaminergic system, and that oestradiol levels act in combination with genetic variants in the dopamine system to affect cognitive measures in an inverted-U manner (Jacobs and D'Esposito, 2011). Experimentally, animal models of TBI have demonstrated gender-specific altered response to catecholaminergic therapies, with female rats displaying little cognitive benefit but excessive motor response when treated with doses of methylphenidate that are therapeutic for males (Wagner *et al.*, 2007).

Genetic variations in the catecholaminergic systems may also influence how these systems are affected by TBI. As discussed above, variability in COMT genotype has significant effects on dopamine status, primarily within the PFC, which is likely to be relevant to cognitive problems following TBI. In addition, genetic variations in the linked ankyrin repeat and kinase domain (ANKK1) and dopamine D2 receptor genes have been associated with differences in cognitive recovery following TBI (Failla *et al.*, 2015). As recently hypothesized by Myrka *et al.* (2015), these innate factors could be used to predict an individual's baseline location on the inverted-U framework for cognitive performance. Hence, patients already lying to the left of the inverted-U for innate or genetic reasons are likely to be more susceptible to the hypodopaminergic effects of TBI and also more likely to respond to dopaminergic medications. In the future, an assessment of these factors for an individual would be usefully incorporated into treatment decisions.

## Conclusions

The cause of cognitive problems following TBI is multifactorial but there is good evidence that disruption to the catecholaminergic neurotransmitter systems is an important cause in some patients. These systems modulate many of the cognitive functions that are impaired following TBI and are themselves affected by TBI. Drugs affecting dopamine and noradrenaline can enhance cognitive impairments in some cases, but treatment response is very variable. This variability is probably due to the heterogeneity of the disease as well as the non-linear effect of the catecholamines on cognitive functions. Therefore, an accurate assessment of an individual's catecholaminergic status is likely to be necessary to direct treatment. There are various molecular, structural and functional imaging methods that could achieve this but further research is required. In particular, further mechanistic work is needed to delineate the exact nature and cause of disruption to the catecholaminergic systems, and the utility of these imaging techniques in predicting response to treatments also need to be established.

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## Supplementary material

Supplementary material is available at *Brain* online.

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