*Psychological Medicine*

**cambridge.org/psm**

## Editorial

**Cite this article:** Savulich G, Menon DK, Stamatakis EA, Pickard JD, Sahakian BJ (2018). Personalised treatments for traumatic brain injury: cognitive, emotional and motivational targets. *Psychological Medicine* **48**, 1397–1399. https://doi.org/10.1017/S0033291718000892

Received: 7 March 2018
Accepted: 20 March 2018
First published online: 11 April 2018

**Key words:**
Outcome; personalisation; precision medicine; traumatic brain injury; treatment

**Author for correspondence:**
George Savulich, E-mail: gjs46@medschl.cam.ac.uk



CAMBRIDGE UNIVERSITY PRESS

# Personalised treatments for traumatic brain injury: cognitive, emotional and motivational targets

George Savulich[1], David K. Menon[2], Emmanuel A. Stamatakis[2], John D. Pickard[3] and Barbara J. Sahakian[1]

[1]Department of Psychiatry and Behavioural and Clinical Neuroscience Institute, University of Cambridge, School of Clinical Medicine, Cambridge, UK; [2]Division of Anaesthesia, Department of Medicine, University of Cambridge, School of Clinical Medicine, Cambridge, UK and [3]Department of Clinical Neurosciences, University of Cambridge, School of Clinical Medicine, Cambridge, UK

Traumatic brain injury (TBI) occurs when an external force to the head alters brain function. TBI is one of the leading causes of death and disability worldwide, with motor vehicle accidents and falls accounting for most hospital admissions. Each year, there are 50–60 million new cases of TBI, which disproportionately affect young men in low- to middle-income countries (Maas *et al.* 2017). TBI is a complex condition characterised by a wide range of physical, behavioural, cognitive, emotional and motivational disabilities. Post-injury effects are not limited to severe TBI and can also present in mild to moderate cases. TBI is one of the most established environmental risk factors for increased incidence of epilepsy, stroke and neurodegenerative disorders including Alzheimer's disease. However, rehabilitation centred on physical therapy of movement and gait after injury often overlooks longer-term changes in mood and neuropsychiatric symptoms. Despite the rising burden of TBI to the individual, their families, healthcare services and society, recruiting patients to research studies remains challenging, with numerous practical and methodological difficulties leading to inadequate sample sizes and high dropout rates (e.g. more than 40%; Dikmen & Levin, 1993). The aim of this Editorial is to identify common barriers between research participation and clinical translation, with a call for more personalised treatment approaches addressing cognitive, emotional and motivational targets to improve management and outcome in patients with TBI.

Individual variation in patient characteristics will inevitably bias the likelihood of research participation. For example, it has been found that those with *more* significant head injuries were more likely to enroll in longitudinal research (McCullagh & Feinstein, 2003). This may reflect the more frequent use of, or perhaps gratitude towards, healthcare services *after* injury, particularly if the research site is at the same location as the clinic or hospital where treated. In terms of participant attrition, particularly for studies with multiple assessments, it has been similarly found that those who continue to participate are more severely ill than those who dropout (Binder *et al.* 1997). It is not surprising that individuals with less cognitive impairment, fewer neuropsychiatric symptoms or better general daily functioning would be more motivated or actively engaged in work or other activities. However, most individuals with mild TBI make a good recovery and may thus have less availability or consider themselves inappropriate participants for research (McCullagh & Feinstein, 2003). Whereas the numbers lost to follow-up are typically reported with reasons, further details of those refusing participation at the first point of contact are almost never provided, mainly due to ethical reasons in which informed consent of non-volunteers is not given.

The collection of screening logs has traditionally been used to address whether the population recruited to a trial are representative of the general population presenting with criteria that satisfy study entry. However, such logs are not always rigorously maintained. An alternative approach, used in the CENTER-TBI study (Maas *et al.* 2015), is to collect contemporaneous anonymised registry data from participating centres. The resources used for such data collection are not extensive, the attendant regulatory burden is low and the quality of data collection is substantially enhanced. Nonetheless, even when successful, such approaches only allow comparison of presenting and recruited populations, and provide no assurance that the recruited cohort will be representative of the presenting population. As such, participation bias of more severe TBI cases could inflate the chances of making a Type 1 error or finding an effect only present in a more seriously injured group (e.g. in neuropsychological studies). On the contrary, it may not be possible to measure any potential benefit of interventional studies (e.g. in cognitive enhancement studies) if participants are too severely ill or if outcome test items are too difficult, thus raising concerns of population generalisability across different levels of injury severity.

This leads to consideration of emotional, motivational and behavioural changes after TBI. Increased apathy, irritability and impulsivity are common but vary depending on the location and severity of the injury. TBI has also been shown to alter functional connectivity underlying emotion regulation (Moreno-Lopez *et al.* 2016), which can contribute toward increased neuropsychiatric symptoms and illness such as depression in over half of patients hospitalised for TBI. Changes in cognition are also prevalent and important indicators of functional outcome (Spitz *et al.* 2012). Neuropsychological studies have indicated that cognitive impairment following mild TBI is most prominent soon after injury, but typically resolves within one to three months (e.g. Binder *et al.* 1997). During the acute phase of recovery, many patients attending a neurotrauma clinic, head injury service or patient support group will foster meaningful relationships with clinical care staff, including assistant psychologists, and may thus be actively recruited to research studies with success. However, those making an eventual full recovery may lose touch or interest in research altogether. Individuals with more severe injuries may also experience persistent cognitive disturbances, often leading to longer-term difficulties reintegrating back into the community or returning to work. As many patients with severe TBI transition into the chronic care pathway, they may be entered into rehabilitation services in which research opportunities are less available, not tailored to the appropriate phase of an injury or do not consider individual variation in clinical presentation. This is especially problematic given the heterogeneous nature of the condition and further reflects the need for more research to better inform personalised treatment guidelines. At present, translation of research into patient benefit requires a much stronger evidence base at each phase of rehabilitation.

In order to improve clinical management and outcome for the individual, more personalised treatment approaches are needed. Firstly, the target population of interest, ranging from acute care to community reintegration, should be specified *a priori* and matched against appropriate study aims and hypotheses. For example, outcome targets after TBI can be physical, behavioural, cognitive, emotional/motivational, personal and/or environmental, but domains of rehabilitative interventions (i.e. restitutional, compensatory and adaptive) are particular to different phases of injury (Maas *et al.* 2017). These may include combinations of different therapies, such as pharmacological and cognitive behavioural interventions, which could also be used for treating comorbid neuropsychiatric symptoms. Secondly, blood biomarkers, genomic characterisation, advanced structural and connectomic imaging and neuromonitoring including individualised intracranial pressure thresholds and multimodal monitoring are key *patient-tailored* approaches that should be prioritised for further development and implementation. Thirdly, new machine learning techniques, such as topological data analysis, also allow for more precise identification of biomarkers underlying outcome (e.g. Nielson *et al.* 2017) and could be useful for specifying treatment options in subgroups of patients with similar characteristics. Fourthly, as innovation in the field of mental health continues to advance, novel non-pharmacological strategies targeting cognition, which emphasise maintaining high levels of enjoyment and motivation, will be critical for participant recruitment and retention (Sahakian *et al.* 2015). Research studies that are overly repetitive or boring will not circumvent the high dropout rate typical of TBI patients, whereas studies utilising new devices or exciting technology-based interventions are more likely to be rewarding. Furthermore, technology allows for the optimal titration of task-related difficulty for the individual participant in real time, thus ensuring motivation and a personalised approach to cognitive improvement. Finally, a shift in focus towards comparative effectiveness research, which compares the benefits of existing interventions between centres, will continue to be instrumental for international collaboration, big-data sharing and identification of best practice for individual patients rather than groups (e.g. Maas *et al.* 2015).

Overall, the above strategies will help personalise treatments for a largely heterogeneous patient group. At present, further research is required to understand the motivation of patients choosing to participate in research studies compared with those who do not; to better classify and characterise TBI at each level of injury severity, particularly for milder injuries and their long-term effects; and to match appropriate, more tailored interventions for each phase of injury. Cognition should be measured as a primary endpoint for clinical trials, and we recommend standardised measures of episodic memory, executive function, processing speed, multitasking, and planning as domains showing previous amenability to improvement. Comprehensive assessment of affective domains would also be useful for evaluating treatment effects on emotion and motivation. These should be assessed alongside novel biomarkers leading toward new drug discovery or non-pharmacological interventions. Novel technology should also be further developed and implemented, with patient and public involvement, to target unmet needs. We believe that the use of technology in applied TBI research, particularly in the absence of evidence-based pharmacological intervention, could improve patient uptake by reducing some of the stigma associated with mental health treatments. Individualised interventions that use combinations of different therapies (e.g. psychological and pharmacological) addressing the complexities of TBI presentation may synergise the effects needed for good psychiatric, cognitive and functional outcomes. Treatment guidelines should be informed by more personalised approaches that consider variations in patient characteristics and injury so that therapies can be targeted for the individual to maximise the potential for recovery for best quality of life and wellbeing. Given the psychiatric and cognitive symptoms, psychiatrists and psychologists have important roles in the personalised treatment and management of TBI.

**Acknowledgements.** This work was supported by the NIHR MedTech and *in vitro* Diagnostic Co-operative and the NIHR Cambridge Biodmedical Research Centre (BRC) (Mental Health Theme and Neurodegeneration Theme). George Savulich is funded by grants from Eton College and The Wallitt Foundation. Emmanuel Stamatakis is funded by the Stephen Erskine Fellowship, Queen's College, Cambridge, UK. David Menon is supported by the NIHR (UK) through the Cambridge Biomedical Research Centre and a Senior Investigator Award, and by a Framework Program 7 award from the European Union.

**Declaration of Interest.** Barbara Sahakian consults for Cambridge Cognition, Peak and Mundipharma.

## References

**Binder LM, Rohling ML and Larebee BL** (1997) A review of mild head trauma. Part 1: meta-analytic review of neuropsychological studies. *Journal of Clinical and Experimental Neuropsychology* **19**, 421–431.

**Dikmen SS and Levin HS** (1993) Methodological issues in the study of mild head injury. *The Journal of Head Trauma Rehabilitation* **8**(3), 419–423.

**Maas AIR *et al.*** (2015) Collaborative European NeuroTrauma effectiveness research in traumatic brain injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* **76**, 67–80.

**Maas AIR *et al.*** (2017) Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *The Lancet Neurology* **16**, 987–1048.

**McCullagh S and Feinstein A** (2003) Outcome after mild traumatic brain injury: an examination of recruitment bias. *Journal of Neurology, Neurosurgery & Psychiatry* **74**, 39–43.

**Moreno-Lopez L *et al.*** (2016) Depression following traumatic brain injury: a functional connectivity perspective. *Brain Injury* **30**, 1319–1328.

**Nielson JL *et al.*** (2017) Uncovering precision phenotype-biomarker associations in traumatic brain injury using topological data analysis. *PLoS ONE* **12**, e0169490.

**Sahakian BJ *et al.*** (2015) The impact of neuroscience on society: cognitive enhancement in neuropsychiatric disorders and in healthy people. *Philosophical Transactions of the Royal Society B* **370**, 20140214.

**Spitz G *et al.*** (2012) Association between cognitive performance and functional outcome following traumatic brain injury: a longitudinal multilevel examination. *Neuropsychology* **26**, 604–612.