

# Who is the surgically resilient individual with traumatic spinal cord injury?

David Graham<sup>1,2</sup>, Guillermo Becerril-Martinez<sup>3</sup>, Jonathan Tang<sup>1</sup>

<sup>1</sup>Faculty of Medicine, University of Sydney, Sydney, Australia; <sup>2</sup>TY Nelson Department of Neurology and Neurosurgery, The Children's Hospital at Westmead, Australia; <sup>3</sup>Department of Surgery, Concord Repatriation General Hospital, Sydney, Australia

*Correspondence to:* Guillermo Becerril-Martinez. Department of Surgery, 1A Hospital Road – Ground West, Concord Repatriation General Hospital, Sydney, NSW 2139, Australia. Email: guillermo.becerril@sswahs.nsw.gov.au.

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## What is surgical resilience?

Does psychological resilience matter in surgery? Surgery is a stressful experience and the psychology of surgery contributes a large component to post-surgical recovery (1-3). Whether viewed from a positive psychological or a humanistic psychological perspective (4), psychological resilience is essentially a “psychological shock absorber” (5). Resilient individuals characteristically have the ability to bounce back from a set-back and will recover—or even thrive—following a traumatic event. They accept circumstances that can't be changed and are able to adapt to significant changes in the environment. They also tend to regulate stressful experiences and find meaning within and grow from the experience. They have purpose, social and family support, and optimism.

Janis observed a wide variability in patient recovery trajectories even among those with the same intervention (6). He proposed that there is a strong psychological mediation of surgical recovery. This has since been observed in a number of observational studies of recovery trajectories (7). Importantly, certain recovery trajectories—so-called resilient recovery trajectories—resolve faster and have better overall outcomes than less resilient trajectories. Indeed the psychological traits of individuals who have resilient recovery trajectories are the same as those of psychological resilience. This is why we have suggested that these individuals have surgical resilience (7).

Psychological resilience involves a reduced response to stress, which has well-described biological effects mediated via the hypothalamic pituitary adrenal (HPA) axis. Stress biomarkers such as cortisol, adrenaline, IL-6

and C-reactive protein are elevated following a stressful stimulus. The long-term effects of cortisol in particular are counterproductive to recovery, and so the impact of resilience on surgical recovery should not be surprising.

## Does resilience matter in spinal cord injury (SCI)?

Traumatic SCI is a catastrophic, life changing event that results in complex physical and psychological challenges (8). Whilst the data is limited in Australia, it is estimated that two people sustain a new injury every day (9). Motor vehicle accidents and falls accounted for 60% of all causes, while males are three times more likely to acquire SCI than females (10). It is estimated that 40% of individuals are readmitted to hospital within 2 years of injury due to secondary complications (11). Once the post-operative recovery period has passed, the ability to adapt after SCI is important to prevent secondary physical and psychological complications.

Early surgical intervention with decompressive surgery has been shown to reduce secondary neuroinflammation and improve prognosis following SCI. In their systematic review of the timing of surgical intervention following SCI, Fehlings and Perrin found that the evidence was limited but they recommended early intervention with decompressive surgery (12). At the time, evidence was emerging that surgery within 24 hours of injury could reduce the length of intensive care unit (ICU) stay and post injury complications. The Surgical Timing in Acute Spinal Cord Injury Study (STASCIS) trial later showed that decompression within

24 hours of SCI is safe and associated with improved neurological outcomes (13). In Australia, clinical trials are currently underway to ascertain the feasibility of hypothermia and early decompressive surgery, and recovery outcomes in traumatic SCI (14,15).

The ability of individuals to successfully adapt after injury has been explored in a number of studies. Some contributing variables included family relationships, social support, and resilience (16-20). Active coping strategies have been found to have a strong impact on individual variance in positive recovery outcomes in patients (20,21). But there remains a significant risk of anxiety and depression following SCI, with a 12-month prevalence almost doubling the general population (19).

### Can we anticipate the early post-surgical trajectory?

While surgery is a stressful experience, it is only one contributor of stress for individuals with SCI. Recovery from SCI is a long process that requires a multidisciplinary approach. Nevertheless, the ability to better predict which individuals with SCI are likely to have an enhanced recovery after surgery would be valuable. Then it would be possible to streamline some patients towards fast track surgical recovery programs while focusing on intensive recovery of other patients. Resilience is essentially a psychological concept with at least 15 psychometric measures available (22). But the fact that resilience seems to modulate a stereotypical activation of the HPA axis raises several related questions. Why do resilient individuals have a reduced stress response? Can we use the understanding to measure resilience using endogenous biological molecules?

Several authors have raised the question of whether such measures can be used in the clinical setting (23). The key biomarkers are neuropeptide Y (NPY), dehydroepiandrosterone (DHEA) and testosterone, and all of them may play a role in psychological resilience. While DHEA and testosterone have diffuse actions, NPY is a particularly unique resilience biomarker that has an interesting history. It is a neuromodulator with a wide distribution in the brain. The early literature focused on the role of NPY in satiety and obesity, but more recent literature suggests that NPY is an anxiolytic agent that confers a higher degree of resilience (24). High levels of NPY are prognostic of a better psychological outcome following trauma, while reduced levels of NPY are strongly associated with increased anxiety levels, post-traumatic

stress disorder (PTSD), major depressive disorder (MDD) and suicide (7). Interestingly, in their studies on US soldiers undergoing survival training, Morgan *et al.* have found that survival training increases the levels of NPY, with associated increases in psychological resilience (24,25).

Since the stress response is essentially mediated through the HPA axis, it is not unreasonable to hypothesise resilience biomarkers may modulate the HPA axis. Early work found that NPY-ergic terminals and NPY receptors are mainly found in the paraventricular nucleus (PVN) (26). The release of NPY into the PVN triggers the HPA axis (27). This role is therefore suggestive of NPY as a potential biomarker for resilience and stress. Based on more recent evidence from animal models, Enman *et al.* suggest a model of how NPY modifies the HPA axis (28). They propose NPY may directly act on three major adenylylation circuits: the corticotrophin releasing hormone (CRH)-ergic or potentially the GABA-ergic neurons of the hypothalamus, the noradrenergic neurons of the locus coeruleus, or via glutaminergic neurons projecting from the basolateral amygdala into the hypothalamus. However animal models show the roles of NPY receptor subtypes do not all have beneficial behavioural effects, with for instance the Y1 and Y2 receptors having opposite effects.

In their review of NPY, Enman *et al.* go further by observing that NPY could in fact provide novel pharmacological therapy for stress-related psychiatric illnesses (28). It potentially has good pharmacological properties: minimal peripheral side effects, few drug-drug interactions, and long-lasting effect despite the short half-life of NPY. Enman *et al.* discuss a number of animal studies in order to lay the rationale for NPY as a pharmacological therapy for stress-related disease and cite two clinical trials that are currently underway. It is clear that NPY has much clinical potential. While NPY has potential for the treatment of stress-related psychiatric diseases, the resilience literature suggests a wider potential when considered from the perspective of psychological resilience (29).

However it is not known whether the pathophysiology of SCI modulates resilience. Damage to the spinal cord not only disrupts sensory and motor pathways, but also the autonomic nervous system. The body's stress response, sympathetic nervous system, and resilience are intimately related. It is not unreasonable to hypothesise that physiology of resilience could be altered after SCI. After all, Verheggen *et al.* have hypothesised that the neural pathway between the hypothalamus, suprachiasmatic nuclei, and pineal gland is damaged in people with a cervical SCI leading

to altered sympathetic regulation of melatonin (30). Given the pathophysiology of SCI has systemic effect on the whole body, it may be worth investigating whether resilience is modulated in individuals with SCI.

### What do we need to do?

We have previously proposed a hypothesis that could test the utility of resilience biomarkers in the surgical context (31). Given the need for early decompressive surgery, and the importance of resilience in adjusting after SCI, identifying the surgically resilient individual with SCI could help streamline patients towards individualised recovery pathways.

The testability of this hypothesis is straightforward and could provide algorithms based on individual resilience profiles. Two broad approaches to establishing the algorithms can be considered (31):

- (I) Prospective approach: resilience profiles of individuals with SCI could be measured in advance to determine the suitability of patients to undergo enhanced recovery protocols. Integrated psychometric testing can also be used to identify risk factors in advance for likely psychosocial issues that may arise during recovery;
- (II) Preventative approach: surgical resilience profiles of individuals with SCI could be modified using pharmacological and non-pharmacological interventions in order to minimise the likelihood of adverse post-surgical recovery trajectories.

Clearly both approaches are complimentary and can be integrated into a holistic post-surgical management of individuals with SCI. Realistic patient expectations managed through effective therapeutic relationships can reduce the magnitude of the initial stress stimulus and increase the likelihood of compliance (31).

As yet, no pre-surgical resilience screen has been published (serum or targeted questionnaire), despite the evidence in support of improved surgical recovery in resilient individuals with SCI (7). A better understanding of which patients are likely to recover faster from surgery following SCI will enable improved selection protocols. Selecting resilient individuals for ERAS programs is therefore an important clinical objective that signals the future of surgical recovery (31). Likewise, less resilient individuals may be at risk of prolonged recovery, but the dose-response relationship is currently unknown. It stands to reason that targeting of recovery interventions tailored to

their needs will enhance their outcomes.

There are many multidisciplinary avenues towards enhancing resilience, such as cognitive behavioural therapy (CBT), mindfulness and prehabilitation (7). However, the opportunity to utilise these approaches in anticipation of trauma or within the 24 hours prior to decompressive surgery is absurd. Their importance during rehabilitation however is clear and the potential use of NPY as a therapeutic agent is a clear adjunct that bears further serious investigation. It is clear that the surgically resilient individual with SCI needs to be better identified, but resilience has wider implications beyond surgical recovery.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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