Final Report

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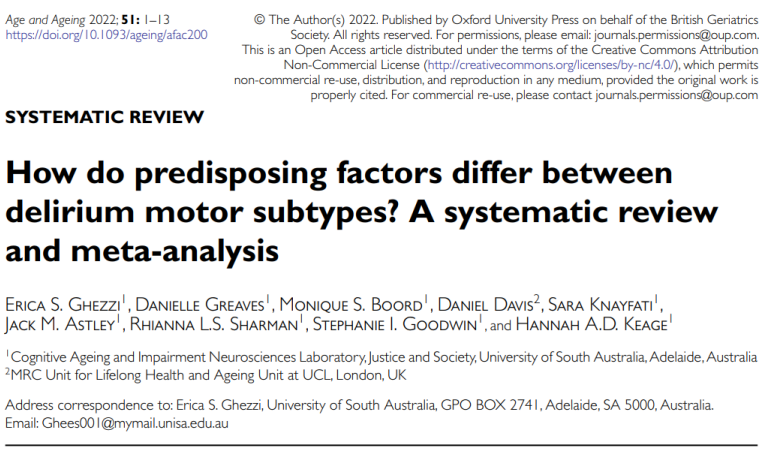
Title of Project:
Understanding why some people develop delirium after surgery

Summary:
Delirium is a neurocognitive disorder occurring in 25% of older adults undergoing cardiac procedures. Consequences of delirium are severe, including a nine-fold increased dementia risk and four-fold increased risk of mortality. Delirium subtypes are typically characterised by motor activity. Hypoactive delirium is characterised by reduced or absent movement and speech and unresponsiveness; hyperactive delirium is characterised by agitation, hallucinations, and increased motor activity; and mixed delirium is characterised by displaying both hypoactive and hyperactive symptoms. Each subtype requires different management and are associated with different outcomes, however investigations commonly study 'any delirium'. Although symptoms overlap, the discriminating hypoarousal and hyperarousal symptoms are markedly different when observed clinically, and therefore different neurobiological processes, and/or, differing extents or patterns of the same processes likely generate these discriminating symptoms.

There were two parts to this project, funded by the Brain Foundation: (i) systematic review and meta-analysis and (2) empirical work.

In terms of (i), we were still affected by COVID research pauses across this grant. We were therefore unable to collect as much empirical data as we would have hoped. We decided to run a systematic review and meta-analysis on clinical characteristics predisposing to developing the different delirium subtypes, which informs out neurophysiological work. This work is now published in *Age and Ageing* (IR=10.7), with the Brain Foundation acknowledged.



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SYSTEMATIC REVIEW

How do predisposing factors differ between delirium motor subtypes? A systematic review and meta-analysis

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Through a robust quantitative synthesis of 61 studies (N = 14,407), we found significant

differences between incident delirium motor subtypes, in terms of their characteristics prior to delirium occurrence. Hypoactive cases were older, had poorer cognition and higher physical risk scores than hyperactive cases and were more likely to be women, living in care homes, taking more medications, with worse functional performance and history of cerebrovascular disease than all remaining subtypes. Hyperactive cases were younger than hypoactive and mixed subtypes and were more likely to be men, with better cognition and lower physical risk scores than all other subtypes. In conjunction with research demonstrating differences by subtype for treatment experience and outcomes, these results highlight the importance of considering motor subtypes in all delirium research.

In terms of (ii), we ran a prospective observational study, including a total of 58 older participants (mean age=75.6 years, SD=7.1; 46 male/12 female). Baseline assessments were conducted in the weeks prior to elective cardiac procedures and included: a four-minute resting state electroencephalography (EEG) recording (2-minutes eyes open, 2-minutes eyes closed), five-minute frequency alteration auditory oddball paradigm recording, cognitive and depression assessments. Peak power, peak frequency, bandwidth, offsets, and exponents were extracted, and event-related potentials (ERPs) were indexed by mean amplitude (P1, N1, P3, and mismatch negativity) relative to deviant and standard auditory stimuli.

We were able to capture neurophysiological markers of delirium risk weeks prior to elective cardiac surgeries in older adults. That is, brain activity patterns differed between those who do and don't develop delirium (in one to two weeks), relative to subtype. Our study provides novel insight into neural pathophysiology of delirium, extending previous work by incorporating more robust measures and investigating delirium vulnerability at the subtype level. Our findings support delirium subtypes as separate entities rather than grouping them together, particularly mixed delirium where its role as a separate pathological entity has been debated. By objectively characterising profiles of neural vulnerability to delirium and its subtypes, risk may be indexed prior to elective surgery and planning for prevention and management can be done in a time where interventions work best. EEG is a promising avenue for delirium prediction and may improve early planning, care management, and early implementation of preventative measures in the preoperative period.

Despite being underpowered due to COVID-19 related recruitment impacts, these findings indicate dysfunction in excitation/inhibition balance in those at risk for mixed and hyperactive delirium and warrant further investigation on a larger scale. There is great potential to improve delirium theory, prediction and clinical management by considering subtypes.

We will be submitting this neurophysiological work to a journal within the next month.

Hypothesis vs Findings
Our results do support our hypothesis that individuals who develop hypoactive delirium predominantly display neurophysiological indices of reduced arousal before surgery. In contrast, those who develop hyperactive or mixed delirium display neurophysiological indices of heightened arousal pre-surgery.

Unanswered Questions
We need to investigate how reliable these measures are. We are currently applying for a NHMRC Ideas Grant to run a larger version of this study in n=350 older patients (cardiac and non-cardiac surgeries).

What these research outcomes mean
Our innovation centres around capturing brain vulnerability for delirium and assessing subtypes. Findings have the potential to target high-cost interventions to those most at risk, reducing delirium cases by a third. Our approach stands to fundamentally change our neurobiological understanding of delirium subtypes and has the potential to improve prognostics and clinical care. Findings, especially as we look to replicate in a larger study, are potentially paradigm shifting, as no other neurophysiological study has looked at the subtype level.