Dopamine's role as an error signal during learning helps drive selective and reliable neuroplasticity over periods of intense, repetitive training as endured during simulation training.

Errors in learning provoke more than just dopamine release. Errors can modulate arousal and attention through other neuromodulatory systems such as those involving norepinephrine and acetylcholine, which can support learning about the error cause, and in turn engage dopamine-dependent neuroplasticity mechanisms.[8,9] In the end, it is a combination of failures and successes experienced during the skill learning curve that triggers neuroplasticity-based learning processes. The control over environment that simulation training provides offers opportunities to tailor training to the underlying neural mechanisms driving plasticity and to provide individualistic and instant feedback to engage neuromodulators, speeding clinical training using simulation.

Rapid Cycle Deliberate Practice (RCDP) is a simulation-based learning modality closely aligned to the 'Live, Die, Repeat' concept.[10] In RCDP the learner repeatedly performs rapid cycles(s) between intentional practice and directed feedback until a level of expertise is achieved. During the simulation exercise the instructor intervenes and interrupts the learner by providing real-time debriefing and feedback when learner errors are encountered, compared with the traditional simulation post-event debriefing. The overall aim is one of continuous improvement upon each iterative cycle in a dynamic learning process. Despite the limited evidence supporting RCDP over traditional simulation methodology, and irrespective of the type of simulation-based learning undertaken by the learner, corticostriatal plasticity is fundamental to learning intentional neuroprosthetic skills.

Looking into the black box of the brain in an attempt to understand the neurophysiological mechanisms underlying corticostriatal plasticity related to simulation-based training is far from complete. We can only provide one of the many hypothetical models within which these neuroplastic mechanisms are governed. Although most of what we know about neuroplasticity originates from animal-based research, translational studies and advancements in neuroimaging technologies and noninvasive brain stimulation will better our overall understanding of the neuromodulators and signalling pathways involved.

In the end, as in the film where the hero only corrects his mistakes through suffering the ultimate failure of death in combat and succeeds by being brought back to life to fight the same battle repeatedly via multiple time loops, simulation-based training provides error-affected learning followed by corrective feedback. This steepens the learning curve, promoting achievement of a level of expertise by attainment of the desired objective, a clinical skill.

Declarations of interest

The authors have no conflicts of interest to declare.

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Tau as a serum biomarker of delirium after major cardiac surgery: a single centre case-control study

Tina B. McKay*, Jason Qu, Feng Liang, Ariel Mueller, Jeanine Wiener-Kronish, Zhongcong Xie and Oluwaseun Akeju

Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

*Corresponding author. E-mail: tmckay@mgh.harvard.edu

Keywords: Alzheimer's disease; cardiopulmonary bypass; cognitive dysfunction; delirium; dementia; phospho-tau; post-surgical complications; tau

Editor-Neurologic dysfunction following major cardiac surgery is characterized by a decline in memory and executive function.[1] This cognitive decline, which approximates Alzheimer's Disease and Related Dementias (ADRD), is evident at hospital discharge, followed by early improvement at six months, and worsening at five years.[1] Worse, the cognitive decline associated with patients who develop postoperative delirium is accelerated.[2] Recent studies suggest underlying patient vulnerabilities contribute to delirium.[3,4] Midlife cardiovascular risk factors have been associated with increased amyloid aggregation in the brain[5] and cognitive impairment later in life.[6] However, a critical unknown is whether major cardiac surgery exacerbates latent pathophysiology underlying ADRD.

The phosphorylated tau isoforms at threonine 217 (P-tau 217) and 181 (P-tau 181) are newly identified systemic biomarkers of ADRD[7] associated with synaptic and neuronal dysfunction and neurodegeneration. Interestingly, total tau (T-tau) and P-tau 181 levels have been shown to be increased

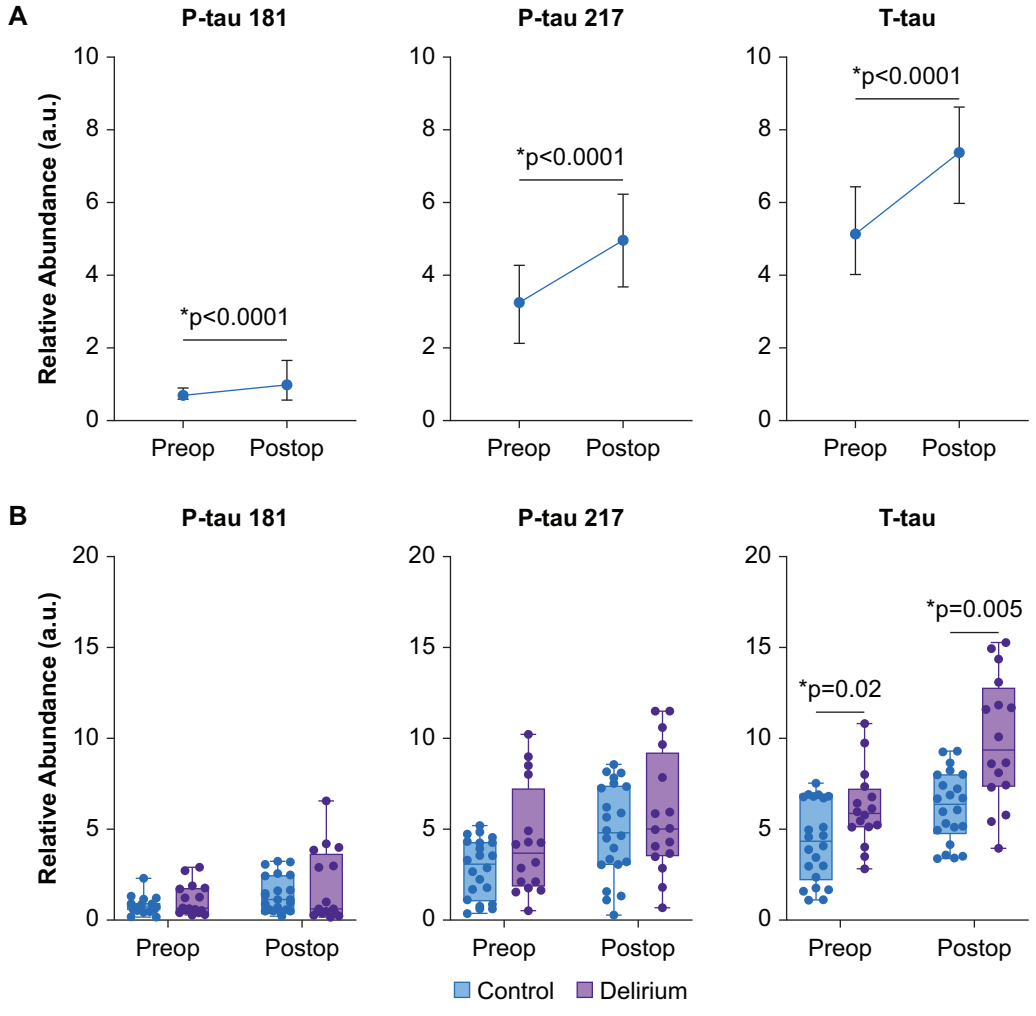

Fig 1. Preoperative and postoperative total tau serum levels are associated with delirium. (A) Relative abundance of P-tau 181, P-tau 217, and T-tau before and after surgery (postoperative day 1, POD1). Data shown as median (95% CI). Statistical significance between preoperative and postoperative levels were determined based on paired t-test. (B) Preoperative and postoperative serum levels in patients with delirium compared to age- and sex-matched control patients. Tau protein serum levels were measured as a relative abundance in arbitrary units (a.u.). Statistical significance was based on an unadjusted univariate model constructed using logistic regression. The values from the multivariable model are adjusted for age and preoperative a-MoCA (shown in Supplementary Table S2).

following major cardiac surgery compared to preoperative levels.[8] Postoperative plasma tau levels are associated with delirium incidence in noncardiac[9] and thoracic vascular surgical cohorts,[10] though it remains unclear if associations between elevated tau levels and postoperative delirium extend to major cardiac surgical populations.

We performed a case-control study of data from patients (n = 38) scheduled for major cardiac surgery with cardiopulmonary bypass to assess relative tau and phosphorylated-tau levels in serum before and after surgery to identify any associations with development of postoperative delirium. The Mass General Brigham Human Research Committee approved this human research study (Supplemental Methods). All participants gave written informed consent. Blood was collected before surgical incision and on postoperative day 1. Patients were screened for postoperative delirium and severity with the Confusion Assessment Method twice daily beginning on postoperative day 1 until postoperative day 3. We used the newly developed nanoneedle technology to measure serum concentrations of tau. Models were created to assess associations between tau and delirium, both before and after adjusting for age and preoperative cognitive status. Odds ratio (OR), area under the receiver operating curve (AUROC), and beta coefficients were used to enable inferences. All analyses used two-tailed hypothesis testing, with statistical significance interpreted at $p<0.05$.

Our study cohort comprised 12 women and 26 men with median age of 70 (range, 60 to 85) yr who underwent major cardiac surgery (Supplementary Table S1). We found that P-tau 181 (mean difference: 0.67, 95% Confidence Interval (CI) [0.4 to 0.95]), $p<0.0001$), P-tau 217 (mean difference: 1.85 [CI 1.35 to 2.34]), $p<0.0001$), and T-tau (mean difference: 2.69 [CI 2.03 to 3.35]), $p<0.0001$) were elevated after surgery (Fig 1A). However, only preoperative T-tau (OR: 1.52 [CI 1.06 to 2.17]; $p=0.02$) and postoperative T-tau (OR: 1.66 [CI 1.17 to 2.36]; $p=0.005$) were associated with delirium (Fig 1B). Moreover, postoperative T-tau was more specific than preoperative T-tau for postoperative delirium (AUROC: 0.81 [CI 0.67 to 0.96] *vs* AUROC: 0.7 [CI 0.53 to 0.87], respectively) and significantly correlated with delirium severity (β coefficient: 0.34 [CI 0.05 to 0.63], $p=0.02$, Supplementary Fig. S1). These results were conserved for models adjusted for age and baseline cognitive function (Supplementary Table S2) and were not affected by surgical admission status (in-patient or same-day admission; Supplementary Figure S2).

In this case-control analysis, we show that serum T-tau, P-tau 217, and P-tau 181 were elevated after major cardiac surgery. Only T-tau was associated with the incidence and severity of postoperative delirium, suggesting a mechanistic link between postoperative delirium and T-tau, upstream of tau hyperphosphorylation and cortical aggregation of these tau isoforms. Our findings suggest that T-tau could be developed as a biomarker for postoperative delirium. Further, they suggest that the perioperative period may be leveraged to enable fundamental new insights into tau regulation and ADRD pathophysiology. Future studies of P-tau 181, P-tau 217, and other P-tau isoforms, including later timepoints beyond postoperative day 3, are expected to enable insights into the longer-term decline in memory and executive function associated with cardiac surgery.

Authors' contributions

Conception: OA, ZX, JW-K, JQ, TBM.
Design: all authors.
Data acquisition: FL, JQ, ZX, TBM.
Data analysis: AM, TBM, OA.
Data interpretation: OA, TBM.
Drafting/revising/approving of final paper: all authors.

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Declaration of Interest

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.04.002.

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Anaesthesia practice in the first wave of the COVID-19 outbreak in the United States: a population-based cohort study

Vassilis Athanassoglou[1], Haoyan Zhong[2], Jashvant Poeran[3], Jiabin Liu[2,4], Crispiana Cozowicz[5], Alex Illescas[2] and Stavros G. Memtsoudis[2,4,*]

[1]Nuffield Department of Anaesthesia, Oxford University Hospitals NHS Foundation Trust, Oxford, UK, [2]Department of Anesthesiology, Critical Care & Pain Management, Hospital for Special Surgery, New York, NY, USA, [3]Institute for Healthcare Delivery Science, Department of Population Health Science & Policy/Department of Orthopedics, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [4]Department of Anesthesiology, Weill Cornell Medicine, New York, NY, USA and [5]Department of Anesthesiology, Perioperative Medicine and Intensive Care Medicine, Paracelsus Medical University, Salzburg, Austria

*Corresponding author. E-mail: MemtsoudisS@HSS.EDU

Keywords: anaesthesia practice; COVID-19; general anaesthesia; nerve block; regional anaesthesia

Editor—The COVID-19 pandemic has profoundly impacted daily clinical practice. Numerous clinical practice recommendations were published during the first wave focusing on guidance to maximise patient and healthcare worker safety.[1–3] However, many of these recommendations were not backed by rigorous evidence,[4–7] sometimes leading to confusion. For example some experts suggested that use of tracheal intubation was preferable to supraglottic airway devices to create a closed system and minimise aerosolisation and environmental contamination, whereas others cautioned that airway instrumentation itself was aerosol generating.[8 9]

It is unclear to what extent these, at times contradicting, recommendations impacted anaesthesia practice in the early stage of the pandemic. We therefore utilised a large national dataset to describe potential changes in practice in the USA, with a specific focus on anaesthesia practice in orthopaedic surgery. We deliberately set out to first pursue descriptive data to understand potential changes in patients served and anaesthesia practice. We hypothesised that in elective orthopaedic surgery during the first wave of the COVID-19 outbreak, use of anaesthetic techniques would differ compared with the year prior. Even though it generally takes years for practice changes to occur, we believe that the extraordinary nature of the pandemic may have warranted an exception to this general wisdom.

After institutional review board approval (IRB#2016-436), we retrospectively analysed patients captured in the Premier Healthcare database (Premier Healthcare Solutions, Inc., Charlotte, NC, USA) who underwent elective total knee or hip arthroplasty (TKA/THA) in the USA. We selected patients admitted during the initial surge of COVID-19 from March 1 to June 30, 2020, as these were the most recent data available to us at the time of analysis. In order to compare this cohort to controls, we selected patients admitted during the same time frame the year prior. TKA was defined based on *International Classification of Diseases*, 9th Revision (ICD-9) procedure code 81.54 or 10th Revision (ICD-10) procedure codes 0SRC0xx, 0SRD0xx. THA was defined based on ICD-9 procedures codes 81.51 or ICD-10 procedure codes 0SR90xx, 0SRB0xx. Exclusion criteria were: unknown sex (n=3), unknown discharge status (n=15), and outpatient procedures (n=7918).

The main outcome of interest was type of anaesthesia on the day of surgery, which was identified from billing codes as described[10]; this was as by general anaesthesia only, regional anaesthesia + general anaesthesia, or regional anaesthesia only. In addition to anaesthesia type, anaesthesia practice was also characterised by perioperative use of NSAIDs, cyclooxygenase-2 (COX-2) inhibitors, and benzodiazepines. We compared anaesthesia practice before and during the first wave of the COVID-19 pandemic.

Results are reported as counts and percentages, and presented in figures. Standardised differences were calculated to compare variables of interests before and during COVID-19. A P-value of >0.1 was considered to represent a meaningful group difference.[11] All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Overall, 87 122 and 13 920 TKA cases, and 64 352 and 11 011 THA cases were performed in the 2019 and 2020 periods of