Although Mrs Jones had stopped responding and appeared to be unconscious, the anaesthetist (correctly) did not assume that she was fully unconscious and continued to talk to her reassuringly, explaining how they were supporting her ventilation. Mrs Jones was probably nicely disconnected and did not care about the outside world, but the anaesthetist should be aware that the patient might be more aware than they appear.

Author contributions

DH and JS contributed equally to the writing of this editorial.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Realising the potential of functional imaging to reveal brain changes after anaesthesia and surgery

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Summary

We highlight the ability of functional brain imaging to detect changes in human brain function, even when changes are not seen in cognitive testing. These imaging changes are plausible as they correlate with known activity changes in carriers of *APOE4*, a genetic variant associated with increased risk for Alzheimer's disease. However, to realise the potential of functional imaging for perioperative neurocognitive disorders, collaborations similar to the Alzheimer's Disease Neuroimaging Initiative (ADNI) with open data sharing will be required. For the practicing anaesthesiologist, we believe that postoperative cognitive issues are important topics to discuss during the informed consent process.

Keywords: Alzheimer's disease; *APOE4*; cerebrospinal fluid; functional MRI; intrinsic functional connectivity; neuroimaging; perioperative neurocognitive disorders; surgery

As the most prevalent genetic risk factor for Alzheimer's disease (AD), the apolipoprotein E4 allele (*APOE4*) is a popular target for research on dementia. Browndyke and colleagues[1] sought to determine the effect of *APOE4* status on perioperative neurocognitive function in a group of patients aged 60 yr or older and scheduled for non-neurologic and noncardiac surgery under general anaesthesia. CSF samples were collected at three time points (preoperative baseline, 24 h postoperative, and 6 weeks postoperative) to measure changes in CSF beta-amyloid (Aβ), tau, and phospho-tau (p-tau) levels. Cognitive and neuroimaging data were collected 1 month before and 6 weeks after surgery. Participants were divided into *APOE4* carrier and non-carrier groups. In a recent issue of the *British Journal of Anaesthesia*, they report that except for the expected lower CSF Aβ in *APOE4* carriers, there were no *APOE4*-related differences in CSF tau or p-tau levels, or their ratios (tau/Aβ, p-tau/Aβ) at any time point, nor were there significant

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postoperative changes in these CSF measures regardless of *APOE4* status. Likewise, they found no *APOE4*-related baseline differences or postoperative changes in global cognition or cognitive domains, and *APOE4* carriers and non-carriers showed similar postoperative changes within specific cognitive domains. There were brain imaging differences between the groups, however: *APOE4* carriers showed greater intrinsic functional connectivity between left/right hippocampus and left angular/supramarginal gyrus, and between posterior cingulate and anterior cingulate gyrus at preoperative baseline. Furthermore, carriers showed greater postoperative reduction in connectivity between left posterior cingulate and left angular/supramarginal gyrus, and between right entorhinal cortex and left inferior frontal gyrus.

The authors stress that these findings provide insight into *APOE4*-related perioperative values, specifically highlighting the preoperative hyperconnectivity and postoperative decrease in connectivity, in contrast to the connectivity increase seen in *APOE4*-negative patients. Perhaps more importantly, the authors state that the fact that brain imaging changes were not accompanied by changes in CSF biomarker levels or cognitive changes highlights the necessity of multidisciplinary approaches for perioperative neurocognitive research.

We applaud Browndyke and colleagues[1] for the ambitious nature of their study; serial CSF sampling in a perioperative patient group is difficult to coordinate and accomplish, the detailed cognitive testing they used is labour and time intensive, and navigating the difficulties of magnetic resonance imaging studies of brain activity adds an underappreciated level of complexity to this well-designed work. We would, however, like to highlight several elements for consideration when extensions of this work are investigated.

Need for cognitive subgroups

Changes in functional brain activity and connectivity across the AD spectrum are non-linear. Many studies have demonstrated the progression of AD from medial temporal lobe/hippocampal hyperactivity/hyperconnectivity at a preclinical stage (in cognitively normal older adults with high Aβ burden[2–5] and in patients with early mild cognitive impairment [MCI][6–9]) to hypoactivity/hypoconnectivity at a later stage (in patients with late MCI and AD[8–10]; for review, see Sperling[11]). Furthermore, brain activity and resting state functional connectivity have been shown to follow a non-linear relationship with cerebral Aβ in cognitively unimpaired older adults, suggesting this transition occurs at the preclinical stage of AD.[12,13] Therefore, when investigating postoperative connectivity changes, it is possible that these patterns also differ for patients at different disease stages, thus the mixing of participants at different disease stages in a study may lead to mixed and conflicting findings. Browndyke and colleagues[1] did not report individual scores on all cognitive tests; doing so would allow consideration of baseline values in each test (as undiagnosed cognitive impairment is common in surgical patients) and would be helpful for meta-analysis (see next section). However, taken at face value, their study almost exclusively used cognitively normal older adults (only one had MCI); therefore, the observed functional changes mostly reflect the effects of *APOE4* and surgery/anaesthesia in cognitively normal older adults, which are likely different from patients with MCI or AD. However, the fact that those with *APOE4* showed connectivity changes similar to the non-linear pattern observed in the progression to clinically diagnosed AD is especially interesting; one wonders what this pattern would look like if those with more advanced clinical disease were imaged. If connectivity simply continued along the trajectories suggested by this study, could a preoperative cut-off value be determined that would signal increased risk of postoperative cognitive issues?

Need for expanded surgical and anaesthetic details

The results of this study do not provide further insight as to what anaesthesia providers should do in the operative room to lessen the chance of postoperative neurocognitive decline (acknowledging that this was not part of the design). Although the authors did not include details on the specific surgeries performed or the anaesthetic drugs used, a review of the cited Markers of Alzheimer's Disease and Cognitive Outcomes after Perioperative Care (MADCO-PC) study[14] and clinical trial registration[15] shows that the general anaesthesia technique used either isoflurane or a propofol–TIVA technique. Comparisons of cognitive index scores and CSF biomarkers did not seem to differ across these two anaesthetic groups, supporting prior findings[16] that CSF inflammatory cytokine levels did not differ as a function of maintenance anaesthetic agent. However, if meticulous drug doses were given along with the full montage of detailed cognitive scores, future meta-analysis could potentially tease out subtle differences for further hypothesis generation.

For practicing anaesthesiologists, the data presented suggest that *APOE4* testing will not independently be of use to categorise the risk of neurocognitive change in cognitively normal older patients. *APOE4* status did not affect global cognitive change, and the trajectory of postoperative cognitive changes was similar for both groups. However, many studies presented as supporting literature by Browndyke and colleagues[1] show evidence that surgery/anaesthesia can lead to neurocognitive issues across the same older population, with changes seen in verbal memory, spatial memory, and executive function. Thus, discussing this possibility with older patients as part of the informed consent process should be done, as well as highlighting that it is unclear if it is the anaesthesia, the surgery, or a combination of both that may be the cause.

Need for expanded use of functional brain connectivity measurements

Previous studies have correlated functional brain imaging with cognitive testing. For example, the authors of this study have reported that global cognitive change after cardiac surgery was associated with functional imaging changes in the posterior cingulate and superior frontal gyrus.[17] It is important to establish the brain areas/networks that are associated with decreased cognitive function, but this most recent study supports a powerful idea – that functional neuroimaging may prove to be a more sensitive marker of brain injury than cognitive testing. This is not a new concept; others have demonstrated the presence of structural and functional imaging changes long after athletes with sport-related concussion are cleared for return to play, for example.[18,19] The modulating effect of cognitive and brain reserve[20,21] is a major complicating factor when correlating subtle brain injury or pathology to outcomes, as cognitive reserve can mask

dysfunction when measured by clinically practical neurocognitive testing. This study clearly demonstrates both *APOE*-related connectivity differences preoperatively and altered trajectories postoperatively, despite equal cognitive testing results across groups. We concur with Browndyke and colleagues[1] and propose that efforts to determine whether specific anaesthetic medications or adjuvant therapies are beneficial or harmful to brain function will require an objective and sensitive biomarker such as brain imaging so that cognitive reserve does not obscure the results.

Need for expanded data sharing and protocol standardisation

Imaging studies are expensive and time consuming. The ADNI was established in 2004 to overcome these issues. Through collaboration and the free sharing of data, ADNI investigators identified biomarkers and helped to determine the factors to consider when recruiting subjects, reducing study and clinical trial cost and duration. We believe that biomarker studies of postoperative neurocognitive disorder would benefit from open data sharing in the same way that AD has. One recent systematic review of MRI use in postoperative cognitive dysfunction and delirium found 10 eligible papers with 269 surgical patients, suggesting a significant amount of data currently exists even without the 52 patients imaged for this study.[23] The research hypotheses and the data collected for investigations into perioperative neurocognitive disorders (PNDs) share many elements with AD investigations. Studies of PND could benefit AD research with relatively small design changes, and the sheer number of ADNI studies would further the PND knowledge base if basic surgical information was included in their data. Additional examples of successful MRI data sharing projects, which include the Human Connectome Project, OpenNeuro, and the International Neuroimaging Data-sharing Initiative, have further shown that the risks of data sharing are small. Concerns of widespread misinterpretation, lack of appropriate credit to those that collected the data, and journal editors rejecting submissions based on secondary analysis of open data have proven to be unfounded.[14,22]

In conclusion, the latest imaging study of Browndyke and colleagues[1] directly illustrates the critical importance of including functional brain imaging in future research into perioperative neurocognitive dysfunction, as it may be one of the only ways to quantify the subtle changes after surgery. However, to really see the full benefit, we must incorporate a greater range in cognitive function and disease, provide full surgical and anaesthetic details, and participate in open sharing of imaging data so that alternative analysis techniques and pooled data can be utilised.

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Authors' contributions

Both authors were involved in conception, interpretation of data in referenced paper, writing the original draft, review and editing of the manuscript, and final approval of the version to be published.

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Declarations of interest

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The drug titration paradox: something obvious finally understood

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Summary

The *drug titration paradox* is an emerging concept in clinical pharmacology. The paradox refers to the observation that when drug is titrated to a specified level of effect in a population of patients, the expected positive correlation between dose and effect is reversed. That is, when titration rather than fixed dosing is used, greater drug exposure is associated with lesser effect, and *vice versa*. The drug titration paradox may have important implications for study design and data interpretation in anaesthesiology investigations, particularly in big data studies.

Keywords: clinical pharmacology; drug titration paradox; pharmacodynamics; pharmacokinetics pharmacology; target-controlled infusion; titration

Drawing on laboratory techniques from having studied inorganic chemistry as undergraduates, the concept of titration applied to the clinical pharmacology of anaesthesia practice is well known to anaesthetists. Trainees are taught from day one about the importance of personalising dose to each patient's needs, titrating drug administration to various signals, such as patient movement, autonomic nervous system activity, haemodynamic variables, and the processed EEG. Clinicians use expert titration to identify the optimal dose, which in terms of a Venn diagram, is at the nexus of the effective, safe, and efficient dose domains.[1]

That increasing drug dose results in increasing drug effect is a core tenant of clinical pharmacology. In most clinical circumstances, the conventional wisdom that more drug translates into more effect holds true, at least until maximal effect is achieved. But when a drug is titrated to a specified effect, this fundamental tenant of clinical pharmacology turns upside down.[2]

This observation seems counterintuitive, and thus the term 'drug titration paradox' arose.[3] In brief, the drug titration paradox refers to the observation that when drug is titrated to a specified level of effect, the expected positive correlation

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