## Title
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**Some heightened sensitivity**

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With the progressive aging of the population, anaesthetists are increasingly faced with geriatric patients. As our patient population greys, there have been regular calls to limit anaesthetic exposure in older patients out of fear of overdose. The current concern over postoperative cognitive dysfunction weighs heavily on some patient's minds, while anaesthetist ponder the significance of the "triple low" as a predictor of morbidity and mortality.[1 2] Anecdotally, elderly patients take a variable, but prolonged, amount of time to recover from anaesthesia relative to younger patients. The open question remains, how and why is the older brain different in its response to anaesthetics?

One possibility is that the older brain is simply more sensitive to anaesthetics; lower doses are required to achieve the same effect. The minimum alveolar concentration (MAC) of volatile anaesthetic required to inhibit movement in response to a surgical stimulus[3] decreases with age.[4] Yet, a series of elegant experiments in ruminants, which have separable cerebral and vertebral circulations, demonstrated that MAC correlates with levels of anaesthetic in the spinal cord rather than with cortical processing,[5] so it is unclear whether the change in anaesthetic sensitivity responsible for the age-related decline in MAC includes a cortical effect. Elderly patients are also more sensitive to propofol for induction.[6] Older rats required higher brain concentrations of propofol to induce 1s suppressions on EEG.[7]

In this issue of the British Journal of Anaesthesia, Chemali and colleagues report on the results of a series of experiments measuring the effect of aging on anaesthetic sensitivity in the line of Fischer 344 rats maintained by the US National Institute on Aging. Paralleling previous work on age-adjusted MAC, the authors found that young adults were significantly less sensitive to isoflurane than older animals (recovering the righting reflex at lower steady-state concentrations of anaesthetic). Moreover, older rats took a longer and more variable time to recover from both isoflurane and from a single bolus dose of propofol. Because aging can affect a number of physiologic parameters, including cardiac output, functional residual capacity, and body composition, it is unclear whether the prolonged recovery is due to some combination of a change in clearance, distribution and/or a change in the central response to the anaesthetic. Finally, the authors demonstrate that methylphenidate, a centrally acting catecholamine reuptake inhibitor, can speed the recovery of older rats to be faster than young rats not exposed to methylphenidate.

The major advance of Chemali and colleagues is the application of a measure of cortical burst suppression derived from the electroencephalogram (EEG), which demonstrates that the change in anaesthetic sensitivity is present in brain.[8] To avoid a confound from the declining voltage amplitude in the EEG signal with aging, the authors developed a sophisticated measure to detect burst suppression rather than the routine voltage threshold of 10 microvolts. This was used to build a time-varying estimate of the probability that the animal was in burst suppression. By developing a continuous, quantitative measure of cortical suppression, the authors are able to show that, at a steady state of isoflurane, aged rat cortex is more sensitive to isoflurane. This demonstrates that the behavioural sensitivity change is a

pharmacodynamic rather than just a pharmacokinetic effect. Finally, the cortical recovery timeframe from propofol parallels the behavioural results, suggesting that the prolonged effect of propofol is due to increased cortical sensitivity.

It is currently unclear what mechanism might underlie a change in global sensitivity to anaesthetics. Both propofol and isoflurane have some GABA-ergic effects, but it is unclear from the current work whether this effect is mediated by some effect on GABA receptors or via another system. On the one hand, mice expressing an isoflurane-resistant knock-in alpha1 GABAA receptor subunit did not change either MAC or the suppression of neuronal responses to noxious stimulation.[9] Yet sensitivity to other GABA-ergic sedatives, including methohexital[10] and midazolam,[11] also increases with aging. Perhaps aging-related changes in GABAA receptor subunit expression or other, compensatory modifications that occur with aging could explain the increased sensitivity to anaesthetics in older animals.[12 13] Alternatively, there could be some downstream effect of aging that explains a generic increase in sensitivity to sedative medications.

But as Chemali and colleagues demonstrate, the anaesthetic state depends upon a balance of cortical suppression and the various arousal systems of the brain. The same group has previously demonstrated that the “reanimation” observed with systemically administered methylphenidate parallels the effect of stimulating the dopaminergic ventral tegmental area. Perhaps the tone of the dopaminergic system sets the anaesthetic sensitivity of the brain and declining dopaminergic tone with aging causes increased anaesthetic sensitivity – this would certainly be a parsimonious explanation with obvious appeal.

This minimal model of anaesthetic sensitivity makes several predictions that can be tested against the data presented in Chemali’s report. Begin by assuming that aging shifts the sensitivity curve to the left and methylphenidate moves it back to the right (Figure 1A). If we look at the mean recovery times, this simple model does surprisingly well. Yet one very salient feature in Chemali’s recovery time data presented in their Figure 1 is that the spread of the recovery times decreases as the recovery times shorten; an alternative way of saying this is that the variance of the distribution decreases as the mean decreases.

Can we capture this spread in the recovery times with this minimal model of sensitivity changes? If recovery from anaesthesia were simply a probabilistic sigmoidal function of effect site anaesthetic concentration, one would not expect any difference in the width of the distribution of times to recovery with a change in sensitivity. Yet the simple addition of first order kinetics to effect site concentration, Figure 1B, leads to a much slower transition through the steep portion of the dose-response curve for the more sensitive population, which will produce a wider distribution of times as the average recovery time increases, Figure 1C. Our toy model is doing surprisingly well.

One observation from the authors' data in their Figure 1, however, stands in stark contrast to our model prediction. For all groups except the older rats given methylphenidate, the amount of variance in the time to recovery changes in parallel with the mean time to recovery. The recovery times in aged rats given methylphenidate are less variable than in aged rats given only propofol, but substantially more variable than in younger rats given only propofol, who take longer to wake. Yet our simple model that combines a sensitivity change with pharmacokinetics would predict the variance in older rats given methylphenidate to fall between the young rats given propofol only and the young rats given propofol and methylphenidate The failure of this prediction suggests that age-related shifting the dose-response curve of general anaesthetics that is opposed by methylphenidate within a single pathway is insufficient.

Indeed, even Chemali and colleagues' careful characterization of anaesthetic sensitivity is incomplete. Kelz and colleagues have definitively demonstrated that recovery from anaesthesia is not simply due to washout of anaesthetic agent, as the sensitivity curve for induction and recovery are shifted versions of each other, with induction taking the role of the blue curve and recovery taking the role of the black curve in Figure 1D.[14] Kelz termed this tendency for the awake brain to remain awake and the anaesthetized brain to remain anaesthetized "neural inertia". Given that Chemali and colleagues only examined the recovery arm in their experiments, it remains an open question as to whether aging shifts the induction curve in parallel to the recovery curve, or whether the degree of neural inertia in the aged brain changes.

The presence of neural inertia is a form of state path-dependence, known generically as hysteresis. A simple two-state model that can capture anaesthetic hysteresis incorporates two different energy wells, one well for the "awake" state and one for the "anaesthetised" state, separated by an energy barrier. The probability of crossing the barrier, one measure of anaesthetic sensitivity, is a function of the depth of the well and the kinetic energy of the particle (Figure 1D). Because the two wells can each change depth at different anaesthetic concentrations, the probability of crossing the wall in one direction need not be the same as the probability of moving in the opposite direction. The presence of neural inertia dictates that at least this minimum model is necessary to capture the brain's sensitivity to anaesthetics. Moreover, this offers more parameters that could affect anaesthetic sensitivity to explain the interaction of methylphenidate with aging; perhaps methylphenidate selectively affects the kinetic energy of the particle without changing the depth of the energy wells.

Developing a better predictive model of what governs behavioural state changes in the brain will require much more quantitative data. The technique employed by Chemali gives us more useful data points, by adding a measure of cortical suppression to overt behavioural measures. This technique can be exploited for characterizing both induction and recovery and seems to parallel the behavioural changes seen in time to recovery.

Yet it is worth noting that there is a long way between burst-suppression and wakefulness. We have previously reported that there are some characteristic features in brain activity that occur during recovery from anaesthesia, and transitions between these different states reveals a required sequence of states that appear prior to recovery[15] Are other EEG activity patterns that occur at intermediate anaesthetic doses also affected by aging in the same way as burst-suppression, with a shift to the left in the curve, or is there a change in the architecture of the network of brain activity states? Perhaps certain rhythms are more stable in old brains, and others simply do not occur. At present we have no sense of how aging impacts the functional effects of anaesthetics on brain activity patterns.

Understanding how the dopaminergic and other arousal systems interact with general anaesthesia will help inform our understanding about rational interventions to facilitate recovery from anaesthetics in aging patients. Given that much of the concern over anaesthesia in the geriatric population could be characterized as recovery gone awry, developing and characterizing an adequate model of recovery that captures the effect of aging is of compelling importance.

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**Figure Legend**

**Figure 1. Panel A.** Curves reflecting different anaesthetic sensitivities, where the $EC_{50}$ for two populations differs by a factor of 100. The population depicted by the blue curve is less sensitive to anaesthesia, and hence remains awake at anaesthetic concentrations that render the black population unconscious. In Chemali's experiment, the black curve corresponds to older rats and the blue curve corresponds to younger rats. **Panel B**. First order drug kinetics yield an exponential decline in effect site concentration over time. **Panel C**. A sensitivity shift with first order drug kinetics predicts longer time to emergence with broader distribution of emergence times. We simulated 10000 animals emerging from anaesthesia with both sensitivity relationships in (A) with the effect site concentration from (B). The distribution of times to waking for the young, less sensitive population (blue) was shorter and narrower than the distribution of times for the aged, more sensitive, population (black). **Panel D**. Emergence is not the reverse of induction. During induction the organism is less sensitive to anaesthetics than during emergence. A simple model to explain hysteresis is that the brain tends to stay in its current state, as though it is trapped in a potential energy well. The probability of switching states is a function of the height of the barrier above the bottom of the well. The arrows show induction (black) and recovery (blue) from anaesthesia that correspond to the transition from one energy well to the other. Note that these transitions do not occur at the same anaesthetic concentration. This minimal model is consistent with the results of Friedman *et al.*[14]