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What anaesthesia reveals about human brains and consciousness

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The combination of general anaesthesia and neuroimaging holds unique potential for catalysing integrative and translational discovery about human brains and consciousness. By spanning molecular, cognitive and clinical neuroscience, anaesthesia provides a bridge from molecules to mind across species.

General anaesthesia ranks among the greatest accomplishments of medicine, and enables thousands of life-saving surgeries every year. In addition to its medical applications, appreciation for anaesthesia's value as a tool to investigate brain function is growing. Anaesthetic drugs disconnect the organism from its environment and transiently inhibit sensation and action[1]. Most anaesthetics suppress the brain's ability to process information, and temporarily shut down one of the fundamental functions of this organ. Combining general anaesthesia with non-invasive neuroimaging, such as functional MRI, offers unique opportunities to study consciousness across species by systematically and reversibly perturbing brain function. Such neural changes observed at the macroscale can be related to downstream effects on cognition and behaviour and upstream molecular mechanisms at the microscale (Fig. 1).

Using anaesthesia as a model

Anaesthetic-induced disconnection from the environment can be achieved by many drugs. These drugs exert their effects on the brain by engaging specific molecular targets, such as binding to specific neurotransmitter receptors. However, as has been shown in vitro[2], anaesthetics vary widely in their respective molecular targets (Fig. 2a). Although most anaesthetics also induce unconsciousness (loss of subjective experience), this is not universal: the environmental disconnection induced by ketamine is often characterized by vivid dream-like experiences, such that subjective experience is detached from the reality of the environment without necessarily being abolished.

Therefore, different anaesthetics offer the opportunity to disentangle normally co-occurring aspects of conscious experience — and the corresponding neural underpinnings. Because anaesthetic drugs have differential effects on behaviour and consciousness that are mediated by shared and distinct molecular pathways, they constitute powerful neuromodulation tools to investigate the dynamic interplay of brain structure and function, and to bridge molecular, cognitive and systems neuroscience in vivo (Fig. 1).

A model for sleep. Some general anaesthetics exert their effects by engaging part of the brain's endogenous pathways for producing loss of consciousness and disconnection from the environment: sleep[2]. However, sleep is less amenable to experimental control

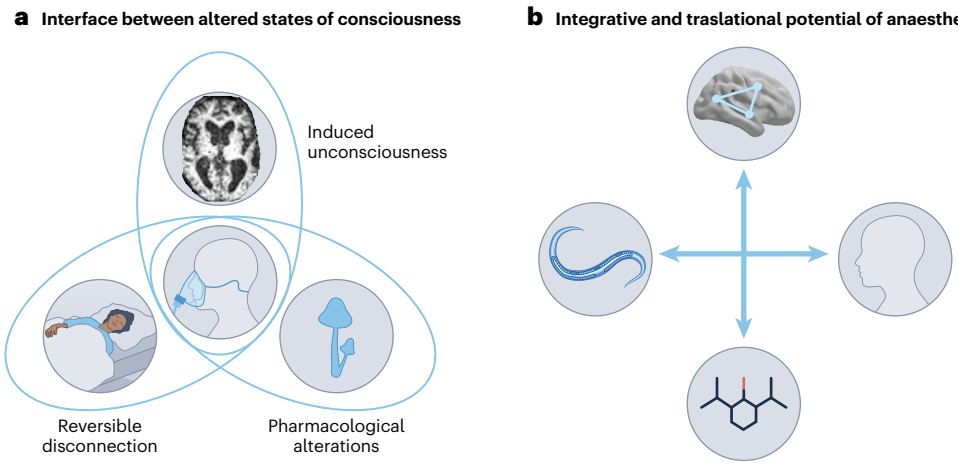

Fig. 1 | The potential of general anaesthesia in neuroscience. a, Anaesthesia acts as an interface between diverse states of altered consciousness. Similar to DOC, anaesthesia is an abnormal state that is characterized by loss of connection with the environment (and often loss of consciousness). Similar to sleep, anaesthesia is a temporary and reversible form of disconnection from the environment, with or without consciousness. Similar to the psychedelic state, anaesthesia is a pharmacological (rather than spontaneous or pathological) way of perturbing consciousness. **b**, Integration from molecules to mind, and translation across species from invertebrates to humans. Anaesthesia acts at the microscale level of molecules, in a way that is conserved from invertebrates to primates, and its effects can be observed at the macroscale level of neural circuits and behaviour.

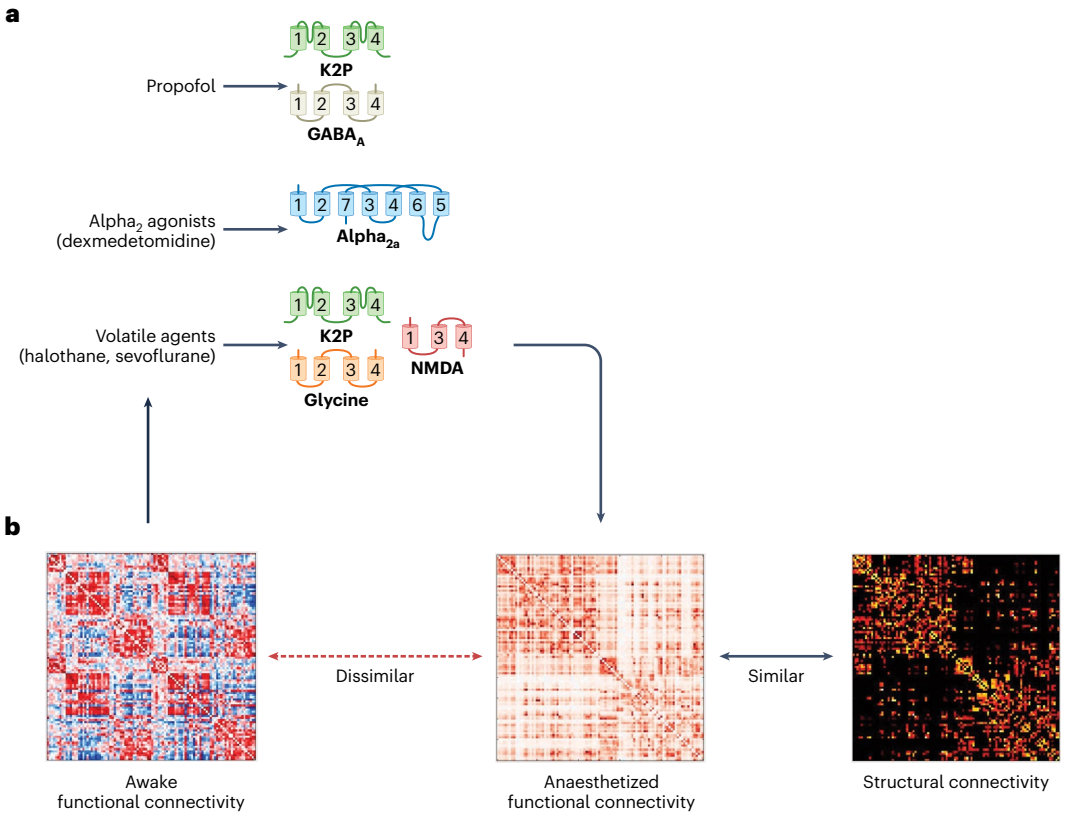

Fig. 2 | Different anaesthetics induce similar increases of structure–function coupling. a, Anaesthetics can act on very different molecular targets. **b**, A key signature of anaesthesia is the increase of structure–function similarity: the pattern of functional connectivity becomes more similar to the underlying structural connections, at the expense of functionally diverse patterns. Panel **a** is adapted with permission from ref. 2, Sage.

than anaesthesia. Neither its induction nor its maintenance is controllable without invasive procedures that cannot be applied to healthy human volunteers. By contrast, it is possible to reach a desired depth of anaesthesia, keep it stable, and achieve controlled emergence. Thanks to this degree of experimental control, researchers have been able to elucidate the neural circuitry for sleep and arousal and its role in promoting or hindering the induction and emergence of anaesthesia[2].

A model for disorders of consciousness. Even in the clinic, the translational potential of anaesthesia extends beyond its role for surgical interventions. The behavioural manifestation of anaesthesia largely overlaps with loss of responsiveness, which is the defining characteristic of disorders of consciousness (DOC). Coma and unresponsive wakefulness syndrome (also known as vegetative state) are commonly known examples of DOC. Such disorders typically arise through brain injury (trauma or lack of oxygen) but vary widely in terms of aetiology, location and extent of lesions, and additional complications. Such heterogeneity in patients with DOC makes it challenging to obtain suitable preclinical models of DOC. Anaesthesia represents an alternative avenue to the same end point of environmental disconnection and has the key advantage that it can be studied in humans, because — unlike brain injury — it is fully reversible. Having a human model of DOC means that language can be used to report on subjective experiences, which is a central part of consciousness research.

Anaesthesia not only matches the lack of behavioural responsiveness in patients with DOC, but also reproduces key neural signatures of this devastating phenomenon (despite arising from temporary changes in neuromodulation, rather than permanent anatomical damage)[3,4]. One key signature of anaesthesia is that it increases the similarity between functional connectivity (the pattern of correlations between regional brain signals, as measured from functional MRI) and structural connectivity (the underlying white matter pathways that physically connect regions, as quantified from diffusion MRI tractography)[4,5]. This increased structure–function similarity occurs because during wakefulness, regions can interact even if they are not directly connected — something that occurs more rarely in the anaesthetized brain (Fig. 2b). Consequently, anaesthesia decreases the diversity of functional configurations that the brain spontaneously visits, and limits it to a more constrained repertoire[4,5]. This phenomenon is consistent with the idea that during wakefulness, the stream of consciousness guides the sequence of brain patterns that we visit. Under anaesthesia, brain activity is instead rudderless and just follows the path laid out by anatomical connectivity.

Crucially, the increased structure–function similarity and diminished repertoire of functional patterns observed in anaesthetized humans are also shared by patients with DOC[3,4]. Anaesthesia provides a way to study these phenomena in humans, and with full experimental control. Patients with DOC only rarely emerge from their condition, which adds to the challenge of identifying ways to accelerate or catalyse recovery. Because emergence from anaesthesia can be closely

controlled, it also provides an avenue to investigate how a disconnected brain comes 'back online'. If there are specific regions that ignite this process or pharmacological interventions that accelerate anaesthetic emergence, they may be suitable candidates for therapeutic interventions in patients with DOC[6]. Therefore, anaesthesia serves not only as an indispensable clinical tool for surgery, but also as a catalyst of discovery in clinical neuroscience.

Comparison with psychedelics. In addition to illuminating sleep mechanisms and mimicking neural and behavioural aspects of DOC, general anaesthesia can also provide a background to understand other kinds of pharmacological alterations of consciousness — notably, the radically altered states of consciousness induced by psychedelics such as LSD and psilocybin ('magic mushrooms'). Direct comparison of several anaesthetics and psychedelics has revealed that they engage the brain's numerous neurotransmitter systems in largely opposite ways[7]. Psychedelics have been shown to reduce the similarity between functional and structural connectivity, which is the opposite of what observed in anaesthesia or DOC[3]. Anaesthesia and DOC diminish the diversity of functional brain patterns, whereas psychedelics induce the brain to visit a broader functional repertoire and produce a variety of unusual subjective experiences (including hallucinations)[3]. Thus, anaesthesia and psychedelics provide opposite, reversible ways to manipulate the structure–function relationship in the human brain in vivo. As anaesthesia shares many of the behavioural and neural manifestations of DOC, assessing the effect of psychedelic administration on awakening from anaesthesia could be of considerable interest as potential stepping stone towards developing new treatments for DOC.

Using anaesthesia across species

Translational potential. The isolation of an organism from its environment — both in terms of sensation and action[1] — is arguably one of the most extreme possible perturbations of behaviour. Although different species have evolved unique ways to respond to their specific environments, the complete lack of response induced by anaesthesia is arguably equally meaningful across animal species.

The presence of a shared end point across species is especially fortunate from a translational perspective because it is not only the effect of anaesthesia that is shared across different species, but also its cause. The same drugs (for example, volatile anaesthetics) are effective on humans, other mammals and even invertebrates[1]. Research has shown that despite having different molecular mechanisms (Fig. 2a), many anaesthetics will induce increased structure–function similarity (Fig. 2b) and a constrained functional repertoire in humans, macaques and mice[4,5,8]. Studying both the same anaesthetic across species and different anaesthetics in the same species offers a path towards the goal of isolating neural effects of anaesthesia that generalize across both species and drugs.

The combination of the same perturbation (exposure to a drug) having the same behavioural effect (disconnection from the environment, as indicated by unresponsiveness) across a wide range of species means that anaesthesia has excellent translational value as a tool of both neuroscientific and clinical inquiry. Neural correlates established in humans can be probed for their causal relevance in animal models that are more amenable to invasive manipulation (for example, intracranial stimulation, administering receptor blockers or antagonists or genetic knockout). Recent studies provide convergent evidence that electrical stimulation focused on the thalamic central nucleus can induce awakening in anaesthetized macaques, despite continuous drug infusion[6]. Crucially, structure–function decoupling was also restored, which suggests this approach as potential therapeutic target for DOC (given its ability to reverse both behavioural and neural features that anaesthesia shares with DOC).

Observing the emergence of interspecies and interindividual differences. Paradoxically, the regions of the human brain that are most affected by anaesthesia are also those that are most evolutionarily recent and most human-specific in terms of gene expression and cognitive function[7]. Although the neural and behavioural effects of anaesthesia are strongly conserved across species, specific regions demonstrate differential susceptibility to anaesthesia in a manner that highlights evolutionary differences across species.

A recent non-peer-reviewed preprint suggests that under general anaesthesia, human functional connectivity is not only less distinct from the underlying structural connectivity, but also less distinctive across individuals and less distinctive between humans and macaques[9]. Functional connectomes obtained from awake individuals can be used as 'brain fingerprints' to distinguish individuals from each other. However, brain fingerprinting becomes challenging when trying to tell apart anaesthetized individuals[9]. Anaesthesia suppresses what makes each of us unique: the specific patterns of thought and feeling of our personal stream of consciousness, as reflected (however imperfectly) in the ongoing interactions between brain regions. The future study of controlled emergence from anaesthesia may represent a way to observe 'in real time' the gradual emergence not only of consciousness, but also of what makes us unique as a species and even as individuals[10].

Conclusion

General anaesthesia is not only vital for clinical practice, but also well-suited for brain research: it is highly reproducible, fully reversible (unlike DOC) and amenable to precise experimental control (unlike spontaneous sleep). As its effects are robustly conserved across species, anaesthesia combines translational potential with the experimental accessibility of nonhuman animals. Finally, anaesthesia is also emerging as a means of illuminating interspecies and interindividual differences.

The time is ripe for bringing together molecular, cognitive and clinical neuroscientists to seize the unique potential of anaesthesia in developing an integrative understanding of brain function and human consciousness across levels of investigation, from the microscale to the macroscale.

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Competing interests
The author declares no competing interests.