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General anaesthesia as fragmentation of selfhood: insights from electroencephalography and neuroimaging

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TITLE: General anaesthesia as fragmentation of selfhood: insights from electroencephalography and neuroimaging

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SUMMARY

Selfhood is linked to brain processes that enable the experience of the person as a distinct entity, capable of agency. This framework naturally incorporates a continuum of both non-conscious and conscious self-related information processing; and includes a heirarchy of components such as: i) awareness of existence (core self), ii) embodied self (sentience), iii) executive self (agency/volition), and iv) various other higher-order cognitive processes. Consciousness relates to, but is not congruent, with selfhood; understanding the processes required for selfhood can explain the partial consciousness seen in anaesthesia. Functional brain imaging and EEG studies in sleep and general anaesthesia have shown differential effects of anaesthetic drugs on various specific self-related functional brain networks. In particular, drug-induced selective impairment of anterior insula function suggests there might be a crucial difference between anaesthesia and natural sleep when it comes to the salience network. With increasing concentrations of anaesthesia, it is not uncommon for patients to become depersonalised – i.e. to lose sentience and agency – but retain many higher-order functions and a disembodied self-awareness, until quite high concentrations of anaesthesia are reached. In this respect, general anaesthesia differs significantly from physiological sleep; where it appears that loss of agency and sentience parallel, or lag behind, the decrease in self-awareness. Interestingly, connectivity within the posterior brain regions is maintained even to quite high concentrations of anaesthesia, potentially representing a pathognomonic marker of the core self that possibly is involved in maintaining a reduced energy-state of homeostasis. (word count 239)

KEY WORDS

Anaesthesia, Electroencephalography, Neuroimaging; Self; Awareness

The absence of consciousness during general anaesthesia is usually inferred by loss of behavioural response to command or absence of explicit recall. However during progressive deepening of general anaesthesia many patients may stop responding but still retain some subjective sense of existence[1]. Because of the strong amnesic effects of the anaesthetic drugs, the actual incidence of 'partial consciousness' – where the patient still has subjective experience but is somewhat dissociated from the environment and from self – is unknown but possibly quite common. A summary of these potential mental states is presented in Table 1. Patients' postoperative reports of intraoperative experiences (i.e. awareness with recall (AWR)) typically involve auditory and somatosensory perception and, more rarely, sensations of disembodiment; with widely varying degrees of pain perception, ranging from the most extreme distress to a state of total analgesia and disinterest [2]. Additional evidence for incomplete unconsciousness is provided by the occurrence of implicit memory formation [3] and intraoperative dreaming [4]. Intraoperative wakefulness may be determined by a volitional response to a command; which can be seen in either non-paralysed patients, or during an isolated forearm test (IFT). Typically, these patients are in a passive and an apparently pain-free state, but do not show spontaneous motor responses. This depersonalised state may be characterised by a feeling of detachment from the surroundings and an inability to attach appropriate significance to sensations[5]. We term this state of undistressed wakefulness as "anaesthetic depersonalisation", and early data from neuroimaging studies show a functional brain imaging signature consonant with a pattern of interoception suppression (as described in more detail later), which fits with very recent concepts put forward by Craig[6].

Apart from the presence or absence of amnesia, there is a large amount of overlap between awareness with recall and intraoperative wakefulness reports. Therefore in this paper we adopt a simplified pragmatic classification of clinical descriptors: (1) awake distressed, (2) undistressed wakefulness/depersonalisation, (3) dreaming and (4) a state of oblivion. We also assume that – around the point of loss of behavioural responsiveness to verbal command – the brain is in a labile, lightly anaesthetised state on the cusp of wakefulness; sometimes responding to a sufficiently salient command (like the patient's name) and sometimes failing to respond. We assume this state is often similar to that seen when there is a positive volitional response in an isolated forearm test. The question arises: "What are the active neurobiological processes that subserve or facilitate this 'tipping point' to awareness?" and conversely "What processes are switched off or dampened in this 'twilight zone' around the point of ceasing to respond?"

<< Table 1 near here >>

Why introduce the concept of selfhood rather than consciousness?

In 1847 Oliver Wendell Holmes first suggested we use the word "anaesthesia" to describe the state of surgical patients under the influence of ether. By the use of this word he explicitly defined the patients as having "loss of perception/sensation" not "loss of consciousness". However discussion about the central nervous system effects of general anaesthesia invariably turns on the effects of these drugs on consciousness, by which we usually mean "phenomenological consciousness"; commonly defined as a subjective experience of awareness. It has been proposed that a continuum of consciousness can be captured by describing gradations in: (a) *level* of consciousness (i.e. rousability for increasing noxious stimuli), and (b) *content* of consciousness (complexity of subjective experience). The problem with this approach is that it is largely derived from brain injury studies[7], and it is often awkward to fit the particular varieties of anaesthesia drug experience into this schema. Although selfhood is intimately interwoven with consciousness, we would suggest that the framework of selfhood might provide taxonomic precision that could facilitate the understanding of anaesthesia. As described later, it is concerned with feelings that naturally incorporate a continuum of both non-conscious and conscious self-related information processing, and there is a wealth of papers linking aspects of selfhood to specific neuroimaging patterns.

Selfhood has been defined in many different ways, but as an umbrella term it describes the variety of brain processes that underly the experience of the person as a distinct entity capable of self-control and agency. There is a large non-anaesthetic literature suggesting that selfhood can be deconstructed into a number of partially independent components: i) awareness of existence (core self), ii) embodied self (sentience/feeling), iii) executive self (agency/volition), iv) various other higher-order cognitive processes, including meta-cognition/meta-awareness, and v) the knowledge of our autobiographical and social selves (narrative). (see figure 1 and brief definitions in legend to table 2)

Recently there has been a vigorous functional brain imaging research effort to delineate the various brain regions associated with (and perhaps necessary for) aspects of self representation [8-13]. Importantly, the different aspects of selfhood have been shown to consistently correlate with steady-state activity and connectivity in the major large-scale cortical functional networks [14], in particular (1) the anterior and posterior medial cortical regions of the default mode network (DMN) [15, 16]; (2) the lateral fronto-parietal cortical regions included in the executive control network (ECN); and (3) the anterior cingulate cortex (ACC) and insulae that form the major nodes of the salience network (SN) [17]. The overlap between this body of work and that of functional brain imaging in sleep and general anaesthesia allows a natural explanation of partial selfhood in terms of the differential effects of anaesthetic drugs on activity in various specific brain regions; that account for the various reported states of partial consciousness. Our proposed model is hierarchical, consisting of a core self onto which additional components of selfhood are accreted (figure 1). The core self represents the most "primordial" and basic brain mechanisms that are required for a simple animal feeling of existence; without necessarily incorporating any specific perceptions, motor output, or elaboration of conscious content. The idea of core self incorporates the most basic definition of phenomenological consciousness, but raises the intriguing question of whether it is possible to have an unconscious feeling of existence. This state, alluded to by T.S. Eliot in the poem East Coker - "Or when, under ether, the mind is conscious but conscious of nothing", has been reported during emergence from general anaesthesia: "I remember regaining awareness before being able to see, hear, or feel anything. Incidentally, that period of darkness, silence, and lack of sensation was probably the most peaceful experience I've ever had"[18]. Based on such reports, it would seem that varying amounts of additional selfhood components may be present during anaesthesia. These reports are intriguing in light of Craig's recent thinking about selfhood and interoception, where he put forward as an alternative to Descarte's classic "I think, therefore I am", an alternative: "I feel, therefore I am or I feel that I am"[6]. This begs the question what is the relationship between salience, sentience, interoception and awareness. We will explore the relationship of the previously defined components of selfhood to the altered brain activity observed during sleep and anaesthesia in the following sections. In Table 2 we briefly summarise some neural correlates, identified from neuroimaging, that are associated with changes of selfhood complexity, behavioural, and EEG state.

<< figure 1 near here>>

<< table 2 near here >>

The hierarchy of selves: the journey to oblivion and back to wakefulness

In recent years, there has been a plethora of functional brain imaging and multielectrode EEG studies describing the effects of general anaesthetics on steady-state or evoked regional brain activity. Broadly these studies have shown that modest concentrations of propofol or sevoflurane anaesthesia produce changes in the activity and functional connectivity in the ECN and DMN similar to those seen in natural sleep. We note that although the changes are most apparent in the large scale cortical networks, it is quite likely that these changes may, in fact, be primarily driven by brainstem mechanisms[19, 20], although the details of brain stem-cortical interactions are subject of ongoing discovery and debate.

At around 0.5 to 0.7MAC (and equivalent propofol concentrations) anaesthetic drugs primarily affect the *anterior* (i.e. under electrode Fp1) brain regions. There is reduction in cortical responsiveness, and in anterior connectivity to the posterior cortex and thalamus [21-25]. Connectivity between the medial and lateral *anterior* brain regions and the medial *posterior* parietal regions (i.e. under electrode Pz) is lost around the time of loss of behavioural response to verbal command (Figure 2).

In contrast, the connectivity *within the posterior* brain regions is maintained even to quite high concentrations of propofol (e.g. 4 μg/ml). Activity in this posterior medial parietal lobe (i.e. PCC) potentially represents a pathognomonic marker of the core self. It is interesting to think of this network in the context of energy conservation and core homeostastic function[6]. This region remains active even during the EEG delta wave dominant brain activity that occurs in deep slow wave sleep and general anaesthesia. It can be seen as analogous to a 'pilot light' of selfhood; with a few studies suggesting that it is only extinguished once EEG burst suppression is achieved[24, 26].

Again, Craig postulates in his recent book that the progressive integration (or degradation in the case of anaesthesia) of all neural activity – for the purpose of attaining optimal energy efficiency in the control of emotion and behaviour – produces a "representation of homeostatic salience as vivid feelings that are continuously changing in the immediate moment ('now') and – during a discrete period of present time – provides a cinemascopic representation of the sentient self, or the 'material me'", as he puts it. He suggests that the insula cortex within the mammalian brain is a place where interoception or the processing of bodily stimuli generates vivid perceptual feelings and, as such, a subjective image of the sentient self across time. Indeed, the very framework by which we think about how feelings and emotions are made from brain processing is being challenged in novel ways[27], and we must include this new thinking into our understanding of how these experiences are degraded by anaesthetics.

<< figure 2 near here>>

These observations suggest that a progressive loss of complexity of selfhood accompanies this 'posteriorisation' of brain connectivity. Conversely, it is possible to follow a canonical sequence of increasing complexity or maturation of selfhood during the process of emergence back from a deeply unconscious state to wakefulness; and link these states with a growing consistency of changes found in functional brain imaging patterns, although work to date is still somewhat limited [28-30]. As depth of anaesthesia or sleep fades (measured by decreases in the amplitude of EEG slow waves), the anterior medial brain regions such as medial prefrontal cortex (MPFC) start to be recruited. This progressive recoupling of the anterior cortex with the PCC is associated with increasing complexity of selfhood and is manifest as more complex dreams (episodes of internally directed consciousness and some self-awareness). This dream content indicates that the self has been enlarged by some functional higher-order cognitive processes (metacognition) and the regaining of partial sentience (see figure 1B).

As anaesthesia or sleep lightens further, the EEG typically shows smaller amplitude, faster waves [31]. The FMRI signature is that of more active lateral fronto-parietal regions, which is manifest by the presence of self-monitoring and agency (i.e. lucid dreaming) and – when fully awake – attention to external salient events (i.e. connected consciousness, full selfhood). These sleep studies also agree with a number of FMRI studies done in wakeful subjects; which have identified the medial and dorsolateral prefrontal cortex (MPFC and DLPFC), posterior cingulate cortex (PCC), and inferior parietal lobule as being strongly activated when the subject is showing conscious awareness of self [8, 11].

The crucial role of the salience network/insula in anaesthesia

The primary role of the salience network, and more specifically the insulae, is to link the bodily sensations (interoception) with the core self to ultimately drive decision-making and behaviour (i.e "this perceptual sensation is happening to *me*") [17, 23, 32-36]. The salience network therefore plays an important role in controlling and switching activity between the DMN and ECN [17]. Various lesions in different parts of the insula are associated with a wide range of neurological deficits related to sentience (neglect and anosognosia), agency (mutism, aboulia), and loss of risk aversity, loss of addiction and loss of anxiety, [37] as well as sensory changes, like pain (after posterior insula lesions)[38, 39].

There appears to be a crucial difference between anaesthesia and natural sleep when it comes to the salience network. Our previously published data showed that propofol-induced depression of evoked activity in the dorsal anterior insula (and associated disrupted connectivity with the DLPFC and inferior parietal lobule (IPL)) is associated with loss of volitional response to command [23]; occurring at only modest propofol concentrations of around 2μg/ml, and before the characteristic slow waves of deep anaesthesia dominate the EEG . This exaggerated anaesthetic inhibition of the anterior insula cortex has been confirmed in studies by Qiu [40], and Liu [41], is seen alongside inhibition of other subdivisions of the insula as part of the analgesic response to sub-anaesthetic ketamine [42] and remifentanil [43, 44] and is seen as part of the anxiolytic effects of midazolam during anticipation to pain[45].

In a direct comparison of the effects of propofol, dexmedetomidine and natural sleep, Guldenmund et al reported that "thalamic connectivity with key nodes of arousal and saliency detection networks was relatively preserved during N3 sleep and dexmedetomidine-induced unresponsiveness as compared to propofol"[46]. On the basis of these observations, we would suggest that the passive but marginally responsive (i.e. depersonalised) state – seen in patients who show a positive volitional response to an IFT, or who report non-distressing intraoperative events – is a state largely specific to general anaesthesia. These patients may be accurately described as retaining many of the higher-order components of selfhood, but have lost most of their agency and sentience as a result of drug-induced suppression of salience and sentience networks. This state is rare in natural sleep because salience network function is relatively preserved in the *absence* of anaesthetic drugs; this is in agreement with the clinical observations of relatively easy arousal from natural sleep and dexmedetomidine sedation. We suggest that the anaesthetic depersonalised state is caused by the marked "interoceptive-suppression" effect of general anaesthetic drugs. The reasons why the insula cortices, as core regions within these networks, should have hightened sensitivity to hypnotic drugs are unclear. We might speculate that it is the result of localised inhibitory receptor subtypes, or even the result of network topography.

The precise details of drug effects on the interactions ***between*** salience and sentience are not yet fully elucidated, and probably vary widely between patients and with different drug concentrations. Analgesic drugs clearly act at various levels to reduce *salience* aspects via their suppression of stimulus related activity and therefore making the stimuli less salient to the patient. In contrast, imaging work suggests much more complex effects with hypnotic drugs; which can also cause a dose-related but variable, reduction in both salience and *sentience* (i.e. the linkage of stimuli to self and hence affective awareness/interoception)[23]. Interestingly, a meta-analysis of neuroimaging studies suggest two major functional-anatomic subdivisions within the anterior insula relevant to the detection and processing of salient information: a dorsal region active during attention tasks, and a ventral region active during affective experience. Touroutoglou and colleagues[47], examined intrinsic functional connectivity using FMRI data from two independent samples of healthy awake adults and showed that stronger intrinsic connectivity within the right dorsal anterior insula network was associated with better performance on an attention task whereas stronger connectivity within the right ventral anterior insula network was associated with more intense affective experience. It is interesting to speculate how, around the point of loss of behavioural response, propofol specifically reduced the activity and connectivity of the *dorsal* anterior insula network, which would reduce the salience (attentional cognitive awareness) of the stimuli. At these propofol concentrations the more preserved *ventral* insula function might still allow some sentience (affective experience).

Corrollaries for monitoring and anaesthesia expectations.

It is widely assumed that anaesthetic-induced loss of selfhood always follows the predictable "quasi-sleep" trajectory; i.e. amnesia, followed by loss of self-control, then loss of self-awareness and finally loss of volition and agency. On the basis of both the clinical and functional brain imaging evidence, this assumption is not necessarily correct. The demonstrable existence of undistressed wakeful patients (i.e IFT/AWR positive but with interoception-suppression) and the selective effects of light anaesthesia on the insula FMRI activity and connectivity, strongly suggest that it is quite common for patients to lose sentience and agency early, but retain many higher-order functions and a disembodied self-awareness until quite high concentrations of anaesthesia are reached. In this respect general anaesthesia differs significantly from physiological sleep; where loss of agency and sentience parallel, or lag behind, the decrease in self-awareness. This has relevance for both the conduct and philosophy of general anaesthesia, and the design of possible EEG monitors.

If *full unconsciousness* is to be the primary target of general anaesthesia, then it would seem to be necessary to show significant anaesthetic-induced impairment of PCC connectivity [48] – or find a reliable anterior EEG correlate of this state. However if prevention of *patient distress* is an acceptable therapeutic target for general anaesthesia, then achieving a state of interoceptive-suppression, with or without amnesia, may be a sufficient goal. What are the EEG markers of interoceptive-suppression? Although there is evidence from only limited numbers of formally assessed patients, it might be that anterior slow wave saturation and the alpha-delta pattern (and parieto-frontal dys-synchrony) are sufficiently good biomarkers of loss of sentience and agency to preclude patient distress, but more work is needed.

Conclusion

It is a truism that general anaesthesia affects function of the whole central nervous system. We would propose that the concept of selfhood provides a natural conceptual framework that can link the results of anaesthetic-induced changes in the functional neuroimaging of brain regions and networks, to the various altered states of awareness seen in anaesthetised patients. The selfhood paradigm explicitly positions the idea of phenomenological consciousness as being embedded within, and influenced by, a number of subsidiary (usually unconscious) brain processes – such as sentience, salience, and agency.

AUTHORS CONTRIBUTIONS

The authors contributed equally to writing this paper.

DECLARATION OF INTERESTS

CEW and IT are named as inventors on pending patents for perception loss during general anaesthesia and the association with slow wave activity saturation.

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TABLES

Mental state	Condition
Unable to achieve any subjective experience	full unconsciousness
Unable to achieve sustained subjective experience	fluctuating unconsciousness
Subjective experience but no memory	episodic amnesia
Subjective experience but no emotion/pain	alexithymia/analgesia
Subjective experience but no volition	aboulia/akinetic mutism
Subjective experience but distant from body	out-of-body experiences
Disconnected subjective experience with no metacognition	dreaming
Disconnected subjective experience with ability to control and/or reflect on self	lucid dreaming

Table 1. Possible mental states associated with general anaesthesia and associated neurological conditions.

Behavioural or EEG state	Components of Self					Neural correlates			
	Core	Narrative	Sentience	Higher order	Agency	PCC	MPFC	LPFC	AIC
Awake distressed	+++	+++	+++	+++	+++	++	+++	+++	+++
Undistressed Wakefulness	+++	++	-	++	+/-	++	++	+/-	-
Dreaming	++	++	++	++	+/-	++	+++	-	++
Slow wave	++	-	-	-	-	++	-	-	++/-

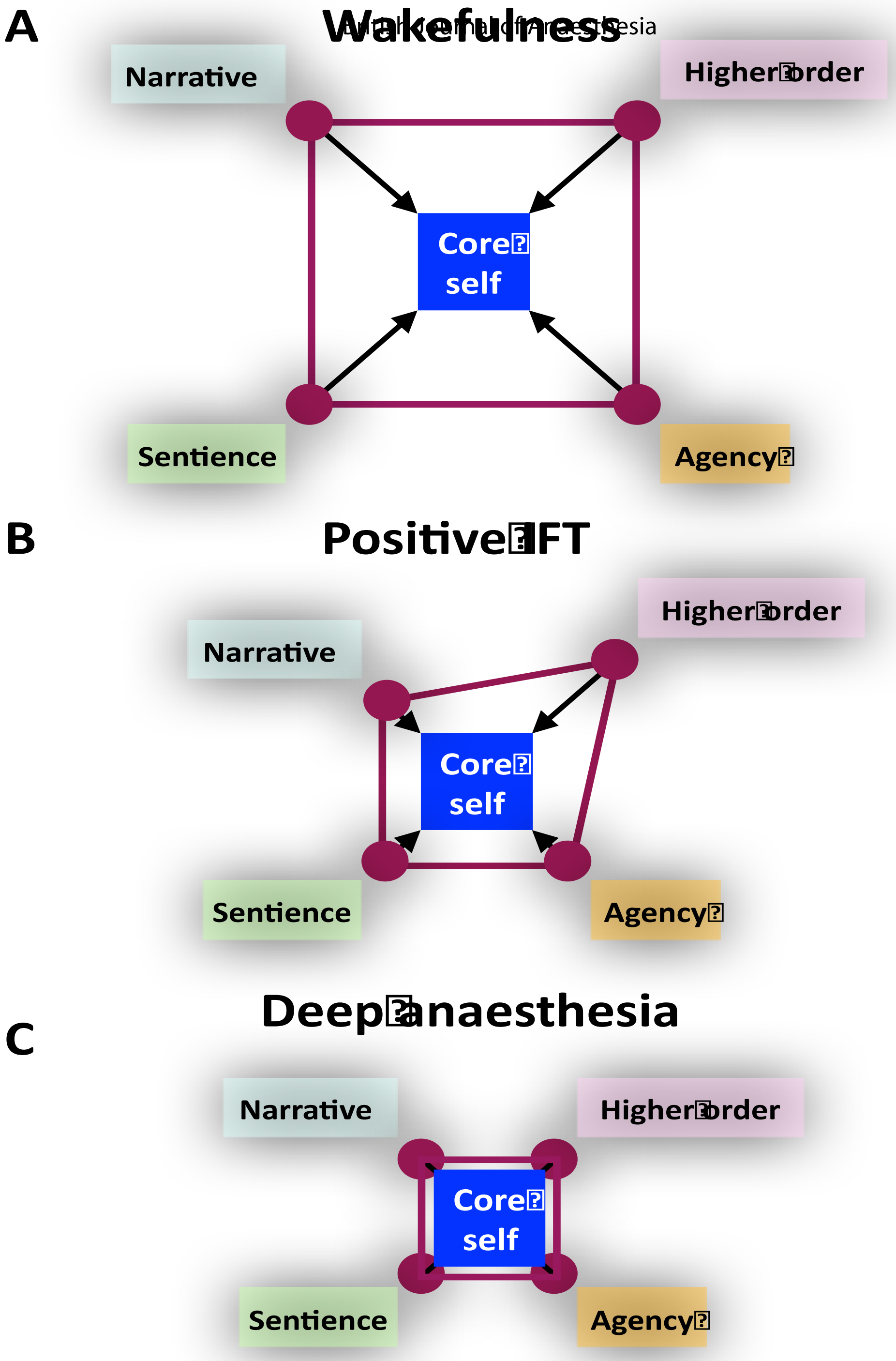
Table 2. Correspondence between the patient state, complexity of selfhood, and functional brain imaging correlates. *Patient state is defined on the basis of clinical, behavioural or EEG evidence. – When compared with an awake and distressed state, Undistressed Wakefulness/Anaesthetic Depersonalisation (i.e. occuring during either a positive IFT or AWR) is associated with marked reduction in the sentience and agency selfhood components; but much less reduction in narrative, and higher order selfhood components. The higher order and agency components are progressively disrupted during the dreaming and with the maximal EEG slow wave activity that occurs during deep sleep and at higher doses of anaesthesia. Namely, there is initially loss of metacognition (lucid dreaming), then loss of self-control/agency/external connection (dreams), and finally loss of even fragmentary dream consciousness (deep slow wave state).The AIC activity is (++) for slow wave sleep and (–) for slow wave anaesthesia. Abbreviations: PCC - posterior cingulate cortex, MPFC - medial prefrontal cortex, LPFC - lateral prefrontal cortex, AIC - anterior insula cortex.*

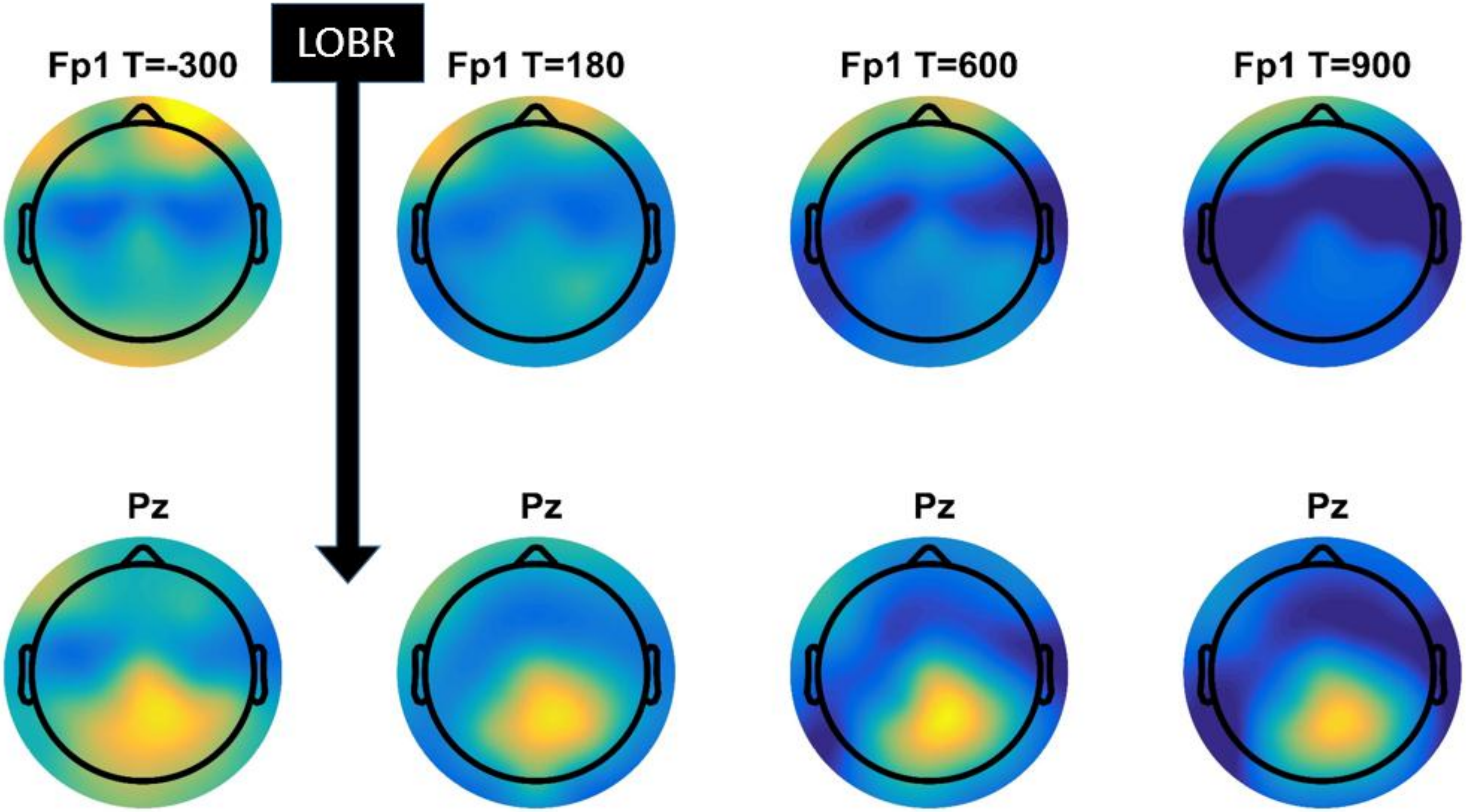
Definitions: *1) Core self = primitive feeling of existence, 2) Narrative self = ability to maintain a sense of continuity of selfhood through time (requires memory function), 3) Sentience = the ability to link* *internal and external stimuli to self, and hence be able to feel them, 4) Higher-order = this includes a variety of self-related cognitive functions such as metacognition (the ability to look on oneself as an object, or being aware that we are aware), self control, morality 5) Agency = the feeling of being able to act in a causal way in the world. It is linked to volition.*

ILLUSTRATION LEGENDS

Figure 1: Conceptual model of selfhood and its application to anaesthesia. *In a wakeful state (A) the core self is combined with: narrative (i.e. memory and knowledge of our social and autobiographical selves), sentience (e.g. pain and emotion - feelings), agency (e.g. volition and willful actions) and other higher order components (e.g. metacognition/meta-awareness). With increasing levels of anaesthesia causing a depersonalised state (B), these components of selfhood are disrupted; but a degree of conscious content remains, allowing positive cognitive responses to an isolated forearm test (IFT). At deeper levels of anaesthesia (C) these selfhood components are reduced entirely – so that only activity in the core self remains.*

Figure 2. Topographic changes in EEG spatial correlations with increasing propofol concentration. *The figure shows changes in functional connectivity as assessed by 1Hz EEG power envelope correlation at two representative electrodes: frontolateral Fp1 (upper row of headmaps), and posterior parietal Pz(lower row of headmaps). Blue colour indicates low correlation(~0.1), and yellow indicates high correlation(~0.8). LOBR indicates time of loss of volitional response to a cognitive auditory word task during experimental propofol induction. Timing (T) of topographic maps are relative to LOBR in seconds. Full details of the analytic methods are described in Warnaby et al*[23]


A
Wakefulness
Narrative
Higher order
Core self
Sentience
Agency
B
Positive IFT
Narrative
Higher order
Core self
Sentience
Agency
C
Deep anaesthesia
Narrative
Higher order
Core self
Sentience
Agency


LOBR
Fp1 T=-300
Fp1 T=180
Fp1 T=600
Fp1 T=900
Pz
Pz
Pz
Pz