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Predictive coding as a model of sensory disconnection: relevance to anaesthetic mechanisms

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A better understanding of the mechanisms through which we perceive our sensory environment is vital for anaesthesiology and consciousness science. Through a pragmatic approach based on tracking afferent signals, we have gradually understood how sensory stimuli are processed from the peripheral sensor, through the peripheral nervous system, into the spinal cord, thalamus, and cerebral cortex. This sensibly heralded the classical, and still dominant, view of sensory processing that focuses on feedforward transmission of sensory information to generate representations of the world around us. Here, perception relies heavily on external inputs driving neural representations of basic stimulus features in lower-order areas of the nervous system. These representations are subsequently elaborated on in successive processing stages, resulting in increasingly abstract representations in higher order cortical regions. Although there is considerable evidence to support this model, it fails to explain many phenomena such as similar physical stimuli producing alternate conscious experiences or illusions,[1]

bistable perception,[2,3] or our ability to shape our own sensory perceptions (e.g. we can control our perception in illusions or use it to 'fill in the blanks', as in the McGurk effect[4] (https://www.youtube.com/watch?v=2k8fHR9jKVM)).

An alternative view is gaining traction, that is predictive coding. In the predictive coding model, higher order brain regions (such as frontal cortex) constantly generate and update hypotheses of the sensory world. These hypotheses are then matched to incoming sensory information, through descending/feedback projections that share these predictions with lower order areas of the sensory hierarchy. If the actual (observed) sensory stimuli do not match the predictions, a feedforward 'prediction error' is generated and propagated up the cortical hierarchy to update the higher order cortical prediction of the world.[5,6] Depending on the reliability of the sensory evidence, the influence of prediction errors on model updating can be regulated, a concept known as precision. For example, under noisy conditions, prediction errors can be down weighted to avoid unnecessary model updates of the predictions. Such a role for modulating the gain of prediction errors has been proposed for the higher order thalamus, such as the pulvinar,[7] which is extensively and reciprocally connected with the cortex, thus ideally positioned to regulate cortical gain.[8,9] An advantage of this model is that it accounts for how sensory processing can occur so rapidly and how illusions, or control of perception, is possible. Predictive coding also explains how we make predictions about our learned sensory environment, for example when we hear a siren, predict an emergency response vehicle and plan to move out of the way; this fits with the hierarchical (and reciprocal) connectivity of the cortex. Hence, given its behavioural relevance and neurophysiological basis, it seems a solid model for further understanding sensory perception.

The clinical intent of anaesthesia is to ablate sensory perception,[10] what we refer to as sensory disconnection, and provide immobility and amnesia.[11] Owing to the intimate link between predictive coding and sensory processing, we argue that predictive coding provides a natural framework through which to study anaesthetic mechanisms. As anaesthetics dramatically disturb neurophysiological processes, it is reasonable to expect that predictive coding will be disturbed. We propose that the four critical elements of predictive coding may be differentially affected in different states of sensory disconnection, such as anaesthesia: (1) higher order cortex prediction generation, (2) feedback of predictions, (3) feedforward prediction error propagation, or (4) estimates of precision. We argue below that sensory disconnection (such as dreams during sleep or sedation/anaesthesia) results from perturbing elements (3), (4), or both; whereas unconsciousness (no experience) results from perturbing (1), (2), or both.

In states of sensory disconnection,[10] we argue that there is an obvious mismatch between the predictions of the external world still being generated in some higher order cortical regions (e.g. 'dreaming of lying on a beach') and the actual sensory environment (a bedroom in the dead of night; Fig. 1). We propose that in sensory disconnection, the mismatch between the incoming sensory information and the generated model in higher order cortex (i.e. the dream) may be explained by impaired feedforward prediction error propagation, estimates of precision, or both (Fig. 1). As a consequence, the model in higher order cortex is not appropriately updated, and thus increasingly deviates from the external sensory environment, leading to disconnected and bizarre dreams. We propose that reductions in norepinephrine may be a critical mechanism of disconnection during sleep and anaesthesia[10] (which is supported by recent evidence[12]). Similar ideas were articulated by Hobson and Friston[13] about rapid eye movement (REM) sleep, another state of sensory disconnection.

Notably, these ideas yield testable hypotheses using sensory paradigms. Years of research have defined the feedforward pathways for differing sensory stimuli, allowing us to test measures of feedforward signalling. More recently, a critical role of higher order thalamic nuclei, such as the pulvinar, in weighting the trustworthiness of sensory evidence emerged.[14] This weighting is akin to precision in the predictive coding nomenclature[7] (Fig. 1). Thus, the predictive coding model provides clear neurophysiological hypotheses that may be tested to expedite discovery of the mechanisms of sensory disconnection.

Some preliminary evidence supports the application of predictive coding theories to the study of sensory disconnection. For example, feedforward connectivity is diminished by propofol sedation,[10] suggesting that propagation of prediction error may be impaired. Reduced activity in the pulvinar nucleus during REM sleep (when the cortex was active)[15] fits with perturbed or diminished precision/weighting of external sensory evidence during (low norepinephrine) sleep-associated sensory disconnection given the role of pulvinar in precision, and its noradrenergic innervation. However, in these studies the conscious state of subjects was assumed and not confirmed. If the subjects were unconscious rather than dreaming, the investigators have studied additional mechanisms not necessary for sensory disconnection. In order to unravel the specific mechanisms of sensory disconnection, we need more thorough descriptors of the conscious state, perhaps through awakenings under sedation[16] (and confirmed with the isolated forearm test[17]) combined with specific testing of sensory responses.

Our interpretation of predictive coding allows us to make further inferences that would not be predicted by the feedforward model of sensory processing. Although we propose that feedforward signalling and weighting of sensory evidence is diminished in states of sensory disconnection, we suggest that there is mismatch between the feedback (higher order cortical) predictions and incoming sensory information (Fig. 1). The afferent subcortical sensory pathway from the peripheral sensor is relatively less affected by anaesthesia, allowing activation of primary sensory regions. However, the net increase in feedback to feedforward signalling leads to *increases* in activity in primary sensory cortex (increased prediction error signalling because of the mismatch in feedback:feedforward information). Although this may appear paradoxical, this explains an oft observed feature of sensory processing under anaesthesia, that of increased (or at least active) processing of sensory information in primary regions.[18,19] We have observed diminished alpha power after transcranial magnetic stimulation in putative (but unconfirmed) states of disconnection of REM sleep and ketamine dissociative anaesthesia.[20] As alpha oscillations are an index

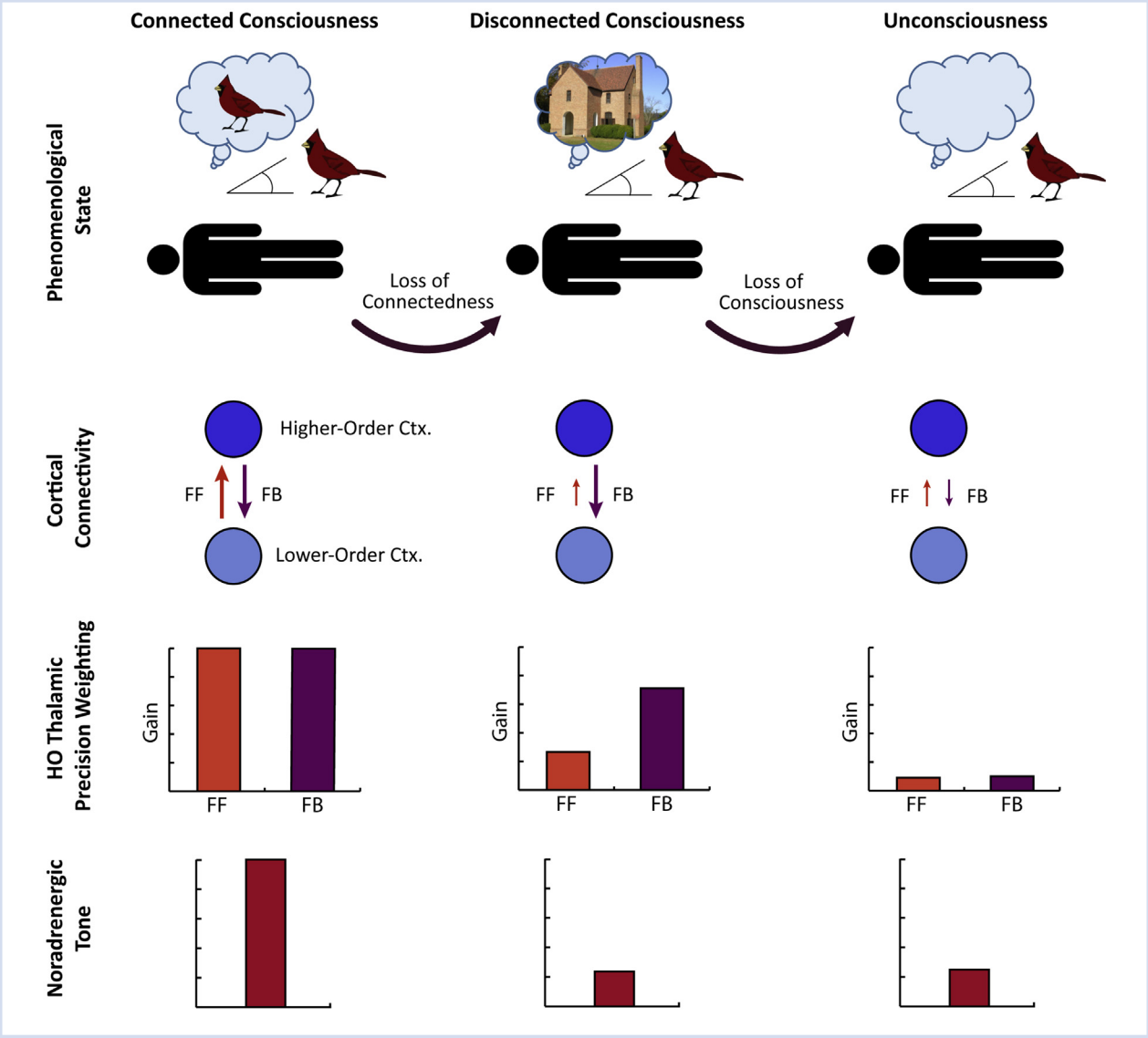

Fig 1. Proposed mechanisms of sensory disconnection according to predictive coding. The phenomenological state of connected conscious (i.e. wake) involves perceiving external stimuli (such as a bird). In the cartoon, the percept in the cloud matches the bird that the eye sees. In contrast, in disconnected consciousness, our experience is unrelated to the sensory world around us (here, perceiving a house not the bird). In unconsciousness, there is an absence of any experience. In connected consciousness, we propose there is balanced, functional feedforward (FF) and feedback (FB) connectivity between higher and lower order cortex. Likewise, higher order (HO) thalamus is well positioned to provide gain to the cortical circuitry, enhancing precision across FF and FB pathways, in the setting of high noradrenergic tone. With sensory disconnection, we hypothesise that FF signalling is diminished, with associated loss of gain from HO thalamus (reducing the precision of the FF sensory information), driven by loss of noradrenergic tone. Finally we propose the transition from disconnected consciousness to unconsciousness is associated with effects on HO cortex (that creates predictions) and loss of FB signalling. Ctx., cortex.

of neural excitability (low alpha power equals high activity and *vice versa*), we interpret this to mean there was increased excitability of cortex in states of sensory disconnection, consistent with the hypotheses mentioned above.

We suspect (though it is unproven) that escalating doses of general anaesthetics make it more likely that subjects are unconscious rather than merely disconnected from the environment. Based on much earlier work, we hypothesise that this transition is accompanied by increased slow wave activity over the posterior cortex, and decreased feedback across frontoparietal regions[10,21–23] (Fig. 1). Our recent data support this notion[24]; however, it is important to note that feedback connectivity is decreased in states where subjects remain conscious[25] and so the degree to which feedback connectivity needs to be decreased to induce unconsciousness needs to be established. In sum, we consider that perturbations to higher

order cortex (that generates predictions) and the feedback connections from those areas may be more important for inducing unconsciousness (Fig. 1). Indeed, based on recent data, posterior higher order cortical areas may be most critical for supporting the conscious state.[26]

Understanding these mechanisms is important for two reasons: (1) monitoring the anaesthetic state and (2) design of anaesthetic regimens. Although improving the high standard of care for the prevention of explicit recall is extremely challenging,[27] rates of responsiveness on the isolated forearm technique remain substantially higher than the low rates of recall,[28] which is at odds with patient expectations about clinical anaesthesia.[29] We need new approaches to depth of anaesthesia monitoring that go beyond preventing explicit recall. Alternatively, perhaps we can modify the way we provide anaesthesia through illuminating how we can modulate the mechanisms of predictive coding, and hence sensory perception.

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Declarations of interest

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