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Finding the starter motor for the engine of consciousness?

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TITLE: Finding the starter motor for the engine of consciousness?

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Back in the days when cars were powered by petrol engines, they required an electric starter motor to rotate the crankshaft of the main engine to get it to draw in the fuel vapour, combust it, and so power the pistons and get moving. In this issue of the BJA, the paper by Nir and colleagues¹ report on resting state functional magnetic imaging in subjects waking from gradually decreasing propofol sedation. As the subject recovered responsiveness, there was widespread activation of both cortical and subcortical brain regions (see table 1 in their paper); and also increases in functional connectivity – that were most marked amongst the various nuclei of the brainstem arousal system. However, more interesting were the *patterns* of changing connectivity. As might be expected, the coupling within the cortex (e.g. between the inferior frontal gyrus and precuneus) showed a progressive linear increase through the emergence period (see figure 4 of their paper). In contrast, the brainstem arousal nuclei showed an unexpectedly transient increase in coupling amongst themselves; which occurred around the point of regain of responsiveness

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3 to verbal command. But this period of co-ordination between these nuclei lasted less than
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5 two and half minutes. It would appear that these nuclei are the starter motors, not the
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7 main engine of consciousness. Once the engine is running these nuclei have no need for
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9 continued synchrony,² so they become more functionally separate and revert to their
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11 ongoing, somewhat independent, roles, such as controlling attention and memory.³
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16 The title of the paper ends with a question mark. As the authors acknowledge, it is
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18 technically difficult to achieve the high temporal and spatial resolution required to detect
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20 activity and coupling in the brainstem, and the results need to be confirmed with higher
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22 resolution methodologies and more stringent multiple comparisons corrections to control
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24 for false positives. Also it is important to note that many real changes in the brain activity
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26 will certainly have been missed – the false negative rate in brain imaging studies is generally
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28 acknowledged to be at least 50%. Absence of evidence is emphatically not evidence of
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30 absence. In particular, it is hard to ignore their failure to find activation of the posterior
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32 medial parietal regions, which have been prominent in most previous similar studies.
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35 Nevertheless, the brainstem findings do have some external support from
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37 electrophysiological work. It has been known for many years that changes in sleep-wake
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39 states are more strongly associated with short-lived intense *phasic* firing rate bursts, than
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41 with step-changes in the background *tonic* firing rates in the brainstem.⁴⁻⁶ Similarly short-
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43 lived bursts in coherence have been shown to occur in cortical recordings during loss of
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45 consciousness.⁷
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53 The arousal nuclei have long been implicated in the mechanisms of both natural sleep and
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55 general anaesthesia. This is the so-called “bottom-up” theory of anaesthesia, which
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57 emphasises the primacy of the brain stem in facilitating consciousness⁸. The theory suggests
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that direct or indirect cortical projection of brainstem arousal activity is necessary in order to depolarise the cortex sufficiently to achieve some consciousness content.⁹ In this model, the cortex is the slave of the brainstem. Evidence comes from many studies showing enhanced emergence from anaesthesia when these brainstem centres are electrically, chemically, or optogenetically stimulated.^{10, 11} Increase in subcortical activity is often greater in magnitude¹² and precedes increased cortical activity and behavioural arousal by a few seconds.^{13, 14} Conversely, drowsiness and coma can be induced by lesions or local inhibition¹⁵ of these brain regions, and also by systemic pharmacological blockade with anti-aminergic, anti-cholinergic, and anti-histaminergic drugs.

At face value the results of Nir and colleagues would support this “bottom up” model; and they go further to suggest that the anatomically and functionally separate arousal systems need to act in concert to trigger awakening. However the reality is more complex. A functioning cortex is clearly a pre-requisite to generate the content in consciousness,¹⁶ and there is also a body of work showing preferential cortical sensitivity to anaesthesia.¹⁷ The efficacy of the various brainstem interventions to increase or decrease consciousness is quite limited. No amount of stimulation of these subcortical centres will wake the animals if the concentration of volatile anaesthetic is greater than about 0.7MAC. Conversely, no true surgical stimulus was attempted with the lesion and inhibition interventions, so it could be claimed that they were sedation studies, not true anaesthesia studies. Any clinician will tell you that you cannot readily achieve a state of surgical general anaesthesia (or even true sleep) simply by blocking these arousal centres; even when giving a combination of antihistamine (promethazine), anticholinergic (hyoscine), anti-dopaminergic (droperidol) and anti-noradrenergic (dexmedetomidine) drugs.

The question arises: What sort of process might cause this increase in activity, but also a sudden – short-lived – surge in coherence amongst the brainstem nuclei? This combination is the characteristic signature of a network undergoing a connectivity phase-transition in its dynamics (see figure 1).^{18, 19} Phase-transition is a term to describe a large (often qualitative) change in a system that occurs in response to a small change in the input controlling it. One such phase-transition is the phenomenon of ‘explosive synchronisation’ within cortical EEG networks, which has been linked with the transition to wakefulness.²⁰ Explosive synchronisation is a generic property of all networks with the appropriate connectivity configuration and – as its name suggests – is characterised by the sudden appearance of relatively long range correlations in activity. Perhaps transient synchrony within the brainstem at the point of waking is evidence of this phenomenon in a subcortical network?

<< figure near here >>

This understanding has some important clinical consequences, as it lies at the core of the difference between general anaesthesia and sleep – why brainstem stimulation does not reverse full anaesthesia, and why states of natural sleep or propofol sedation are not sufficient for surgery. Clearly much more research into the specific dynamics of the interactions of the networks with noxious stimuli needs to be done. But we would hypothesize that in a natural sleep-like state (or dexmedetomidine or propofol sedation), both cortical and brainstem networks are near to phase-transition, so that the necessary brain regional coupling required for consciousness is readily ignited (perhaps first in the brainstem). The engine is primed and waiting for the starter motor. In contrast, for general anaesthesia the network configuration of the cortical functional connectivity is so far from the phase-transition point²¹ so that suitable large scale networks cannot form in response to

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3 brainstem ignition.²² For example, the patient at 0.9MAC who becomes tachycardic and
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6 tachypneic in response to the surgical incision is showing clear signs of localised brainstem
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9 network ignition (at least for the networks controlling respiration and the autonomic
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11 system), but does not wake up. The starter motor is turning, but the carburettor is blocked
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13 and the engine fails to start. In normal physiology the cortex may be the slave to the
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15 brainstem, but the state of anaesthesia would seem to be at least minimally defined by a
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17 cortical veto of the brainstem. Of course better anaesthesia occurs when we also block the
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19 phase-transition in the starter motor/brainstem with appropriate analgesia.
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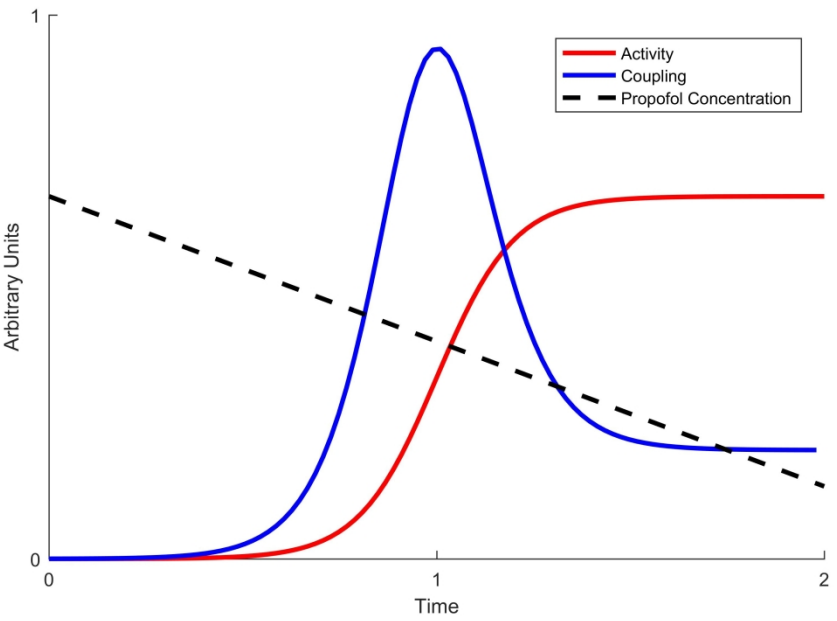
CONTRIBUTIONS: This was an intellectual collaboration. JS contributed to the section on the phse changes and CEW to the sections on the imaging analysis.

CONFLICT OF INTEREST: None

FIGURE LEGEND

Figure 1. Cartoon illustrating a theoretical phase-transition pattern of changes in brainstem network activity and synchrony with changing propofol concentration.

For Peer Review



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