

Brain Functional Connectivity in Wakefulness Predicts Susceptibility to Anaesthesia

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Abstract

There are considerable individual differences in susceptibility to anaesthesia, which will hamper development of reliable biomarkers to track the loss of reportable consciousness during anaesthesia. In the present study, we address this challenge by using functional Magnetic Resonance Imaging (fMRI) to quantify the effect of Propofol-induced changes in brain networks. fMRI data was collected while listening to an engaging narrative and during resting condition. Brain network specialisation, a measure for effective brain network function, was derived before and after mild sedation together with responsiveness to auditory target detection task. Reaction time (RT) was recorded. We found decreased brain system segregation, especially in association system, after mild sedation and such anaesthesia effect only presented during listening to the engaging narrative not under resting state. Particularly, functional connectivity between default mode network and salience network is significantly increased after mild sedation and participants showing lower connectivity at baseline were more likely to become unresponsive after mild sedation, despite similar RT during wakeful state. Our findings revealed the neural correlates under individual differences in susceptibility to Propofol and have the potential to inform improved brain state monitoring under anaesthesia, in future studies.

Keywords: naturalistic stimuli; auditory narratives; system segregation; individual differences

Background

It is a big challenge to develop reliable brain measures to track loss of consciousness after anaesthesia because of significant individual difference in susceptibility to anesthetics (Chennu et al., 2016). To address this challenge, in the present

study, we collected functional Magnetic Resonance Imaging (fMRI) data to explore brain functional connectivity (FC) changes during Propofol sedation and how it relates to individual difference in behavioural responsiveness (i.e., reaction time, RT) to an auditory stimulus.

Naturalistic narratives naturally engage attention as we filter out distraction and integrate our observations and predictions, leading to plot understanding. Thus, they provide an empirical window for measuring the brain's capacity to integrate information over time in response to complex information (Naci et al., 2017; Hasson et al., 2010). In the present study, we used a narratives-listening paradigm to investigate susceptibility of anesthetics.

Methods

Participants

17 (18-40 years; 12 males) healthy participants were recruited in the present study. They were all right-handed, native English speakers, and had no history of neurological disorders. Ethical approval was obtained from the Health Sciences Research Ethics Board and Psychology Research Ethics Board of Western University. The informed consents were obtained for each participant before starting the experiment.

Sedation Procedure

During the experiment, participants were mildly sedated with Propofol. Ramsay sedation scale was used to control the level of anesthetization. Ramsay



level of each participant was evaluated by communication between each participant and 3 independent assessors (two anesthesiologists and one anaesthesia nurse) in person inside the scanner room. During wakeful state, participants were fully awake, alert and communicated appropriately and wakefulness was monitored with an infrared camera placed inside the scanner. During mild anaesthesia state, intravenous Propofol was administered with a Baxter AS 50 (Singapore). An effect-site/plasma steering algorithm was used combined with the computer-controlled infusion pump to achieve step-wise increments in sedative effect of Propofol. This infusion pump was manually adjusted to achieve desired levels of sedation, guided by targeted concentrations of Propofol, as predicted by the TIVA Trainer (the European Society for Intravenous Anaesthesia, eurosiva.eu) pharmacokinetic simulation program. The pharmacokinetic model provided target-controlled infusion by adjusting infusion rates of Propofol over time to achieve and maintain the target blood concentrations as specified by the Marsh 3 compartment algorithm for each participant, as incorporated in the TIVA Trainer software (Marsh et al., 1991). For both awake and mild sedation sessions, participants were asked to perform a computerized auditory target detection task (4 minute), which further assessed anaesthesia level. Participants were asked to press a button with their index finger once they heard an auditory beep, during which they were required to keep their eyes on a fixation cross on the screen. The averaged reaction time (RT) for each participant was extracted for further analyses. Single-subject RT (ms) is averaged over 50 trials requiring the detection of the auditory target, in the wakeful and mildly anesthetized states.

fMRI Acquisition and Analysis

For both awake and mild sedation conditions, there were two sessions: 1) a plot-driven audio narrative lasts about 5 minutes (Naci et al., 2017) was presented in the fMRI scanner to healthy participants and they were asked to simply listen with eyes closed; 2) a relaxing rest condition lasting about 8 minutes with eye closed. fMRI data were acquired on a 3T Siemens Tim Trio system, with a 32-channel head coil. Standard preprocessing procedures and data analyses were performed with SPM8 and the AA pipeline software. In the preprocessing pipeline, the first five scans of each session were discarded, a temporal high-pass filter with a cut-off of 1/128 Hz was applied and movement was accounted for by regressing out

the 6 motion parameters. FC was generated by computing Pearson correlation of the fMRI time courses of 34 regions of interests (ROIs) according to Raichle 2011. All of analyses were conducted by using Fisher z-transformed correlation (Pearson r). Seven networks were defined accordingly, which are default mode network (DMN), dorsal attention network (DAN), executive control network (ECN), salience network (SN), Sensorimotor Network (SM), Visual Network (VIS) and Auditory Network (AUD). Within and between different network connectivity were derived to calculate brain system segregation, a good indicator for effectiveness of brain processing information (Wig, 2017). The equation is:

$$\text{System segregation} = \frac{\bar{z}_w - \bar{z}_b}{\bar{z}_w}$$

in which, \bar{z}_w is within network connectivity, \bar{z}_b is between network connectivity.

Statistical Analyses

Pairwise t-test was conducted to compare FC in awake state with FC in mild sedated state. Pearson correlation analysis was conducted to correlate FC value in awake state with RT under mild sedation. Multiple comparisons were corrected by false discovery rate (FDR correction).

Results

Behavioral results

The reaction time for both awake and mild sedation conditions were showed in Figure 1. We can tell no significant individual difference across participants in awake state while significant variation in mild sedation.

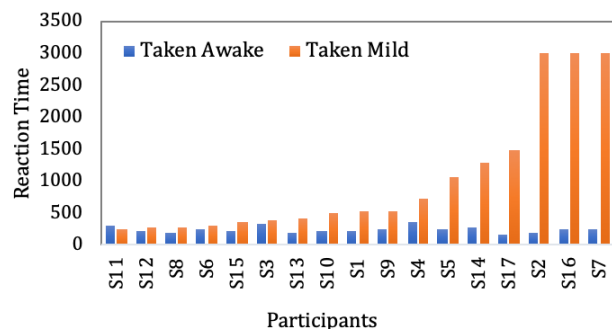


Figure 1. Behavioral response in the target detection task inside the scanner.

De-differentiated brain activity in audio narrative not in resting state conditions

Figure 2 showed that mild anaesthesia has different effects on brain mechanisms underlying loss of external information processing and resting condition. To be specific, in the resting condition, we observed no effect of mild anaesthesia on segregation property over all seven brain networks ($t = 0.159$; $p = 0.857$), which, by contrast, decreased significantly during the audio narrative condition ($t = 4.354$; $p < 0.0001$).

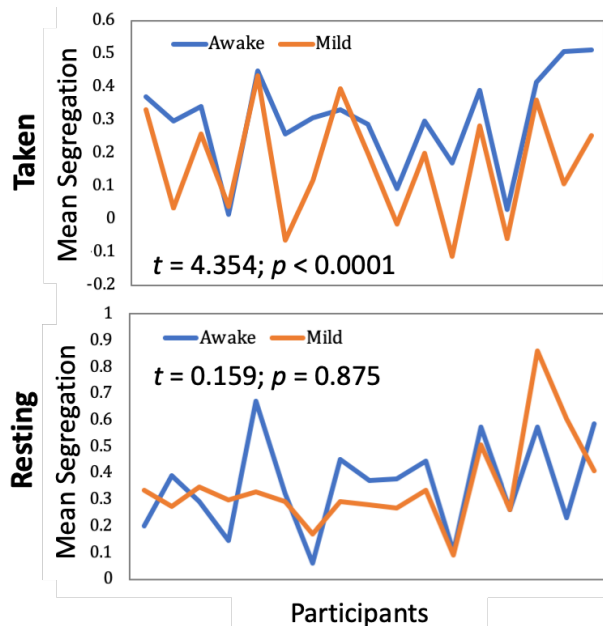


Figure 2. The effect of Propofol on brain connectivity. Propofol shows different effects on segregation property over all seven brain networks during listening to an engaging audio narrative from a suspenseful movie taken (upper panel) and during resting state (bottom panel), with a significant effect on former condition not on resting state.

Sensory-motor system is exempt from anaesthesia effect

Figure 3.A shows that the decreased brain network segregation is derived from significantly increased between-network connectivity ($t = -2.569$; $p = 0.0206$) and unchanged within-network connectivity ($t = -0.490$; $p = 0.6311$). Two brain systems, an association system (DMN, DAN, ECN and SN) and a sensory-motor system (SM, VIS and AUD), were defined to explore the anaesthesia effect. Figure 3.B shows that

association system segregation is significantly decreased after mild anaesthesia ($t = 3.425$; $p = 0.0035$) while sensory-motor system is exempt from such effect ($t = -0.586$; $p = 0.566$).

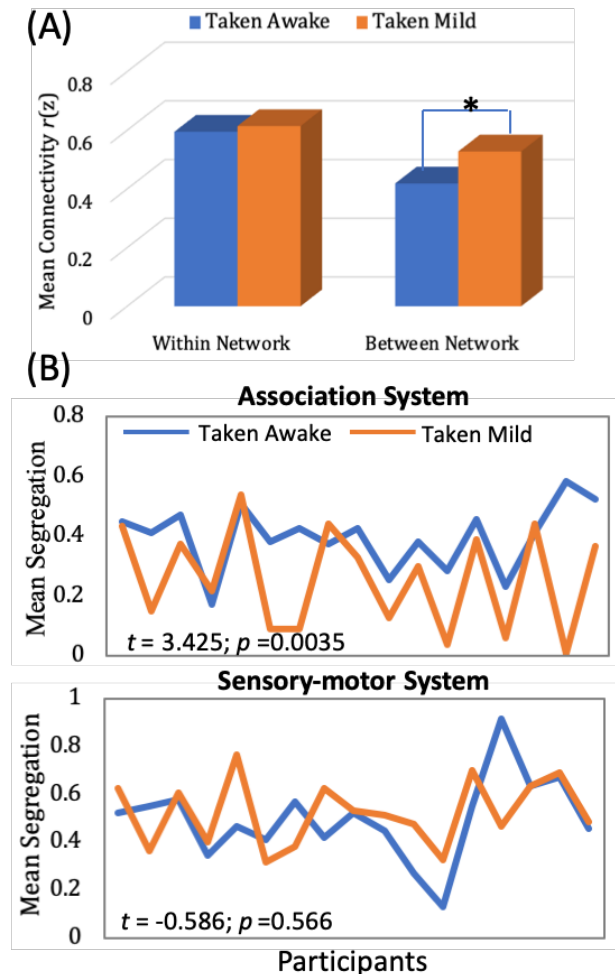


Figure 3. The effect of anaesthesia on different brain systems during an engaging audio narrative. (A) Mean between-network connectivity significantly increased under mild sedation, while no significant change in mean within-network connectivity. (B) Propofol shows different effects on sensory-motor and association systems, with significantly decreased system segregation in the association system, while no effect on sensory-motor system.

Functional connectivity in awake state predicts individual responses under mild sedation state

Figure 4 shows that functional connectivity between DMN and SN significantly increased after mild anaesthesia ($t = -3.405$; $p = 0.004$, FDR corrected) and DMN-SN connectivity of each participant in awake state highly correlated with their reaction time to an auditory stimuli detection task under mild sedation ($r = -0.664$; $p = 0.004$, FDR corrected).

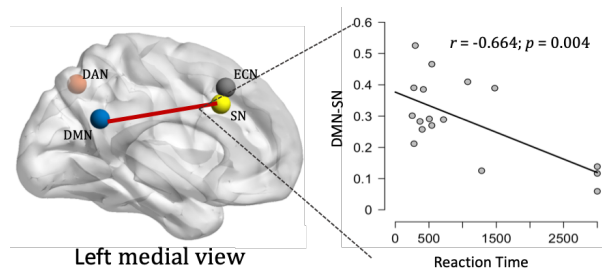


Figure 4. Brain connectivity in association system, in the Taken condition, was significantly affected by anaesthesia. Connectivity in the awake condition in this system predicted individual differences in reaction time under mild sedation. We compared averaged within and between-network connectivity in association system before and after mild sedation. Four nodes shown in the brain are the representations for the four brain networks in the association system. Connectivity between DMN and SN significantly increased after mild sedation (left panel). Pearson correlation between this connectivity in awake state and reaction time (RT) in mild sedation state is shown in the right panel. Abbreviations: default mode network (DMN), dorsal attention network (DAN), executive control network (ECN), and salience network (SN).

Conclusion

Our results showed that the naturalistic narrative is more sensitive for measuring the effect of mild anaesthesia on brain-behavior relationships than resting condition. We found mild anaesthesia disrupted the brain capacity to effectively process external information, which is showed by decreased brain system segregation. We further found the decreased segregation after mild sedation was caused by increased between-network connectivity, especially in association system. In particular, we found that connectivity between DMN and SN significantly

increased after mild sedation and participants with lower DMN-SN connectivity in the awake state showed slower responses to an auditory target detection task under mild sedation. These findings suggest that the DMN and SN interactions are part of the brain mechanism that underlies individual differences in susceptibility to anaesthesia. Therefore, they have the potential to inform improved brain state monitoring under anaesthesia, in future studies. Besides, our results also suggested system segregation is a good measure to quantify the effect of mild anaesthesia on brain function because it can provide information about effectiveness of brain processing information (Wig, 2017).

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