Title

The brain-bases of responsiveness variability under moderate anaesthesia

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Abstract

Anaesthesia combined with functional neuroimaging provides a powerful approach for understanding the brain mechanisms that change as consciousness fades. Although propofol is used ubiquitously in clinical interventions that reversibly suppress consciousness, its effect varies substantially between individuals, and the brain bases of this variability remain poorly understood. We asked whether three networks that are primary sites of propofol-induced sedation and key to conscious cognition — the dorsal attention (DAN), executive control (ECN), and default mode (DMN) network — underlie responsiveness variability under anaesthesia. Healthy participants (N=17) underwent propofol sedation inside the fMRI scanner at dosages of 'moderate' anaesthesia, and behavioural responsiveness was measured with a target detection task. To assess information processing, participants were scanned during an active engagement condition comprised of a suspenseful auditory narrative, in addition to the resting state. A behavioural investigation in a second group of non-anesthetized participants (N=25) qualified the attention demands of narrative understanding, which we then related to the brain activity of participants who underwent sedation. 30% of participants showed no delay in reaction times relative to wakefulness, whereas the others, showed significantly delayed and fragmented responses, or full omission of responses. These responsiveness differences did not relate to information processing differences. Rather, only the functional connectivity within the ECN during wakefulness differentiated the participants' responsiveness level, with significantly stronger connectivity in the fast relative to slow responders. Consistent with this finding, fast responders had significantly higher grey matter volume in the frontal cortex aspect of the ECN. For the first time, these results show that responsiveness variability during propofol anaesthesia relates to inherent differences in brain function and structure within the executive control network, which can be predicted prior to sedation. These results shed light on the brain bases of responsiveness differences and highlight novel markers that may help to improve the accuracy of awareness monitoring during clinical anaesthesia.

Introduction

Understanding how the human brain gives rise to consciousness remains a grand challenge for modern neuroscience. A first step to understanding consciousness is to define what it is not. To this end, anaesthesia combined with functional neuroimaging provides a powerful approach for studying the brain mechanisms that change as consciousness fades (Vatansever et al, 2020; Pal et al., 2020; Varley et al., 2020; Luppi et al., 2019; Demertzi et al., 2019; Mashour and Hudetz 2018; Naci et al., 2018; MacDonald et al., 2015; Sarasso et al., 2015; Stamatakis et al., 2010), and, conversely, that are necessary for realizing human consciousness. Anaesthesia has been used for over 150 years to reversibly abolish consciousness in clinical medicine, but its effect can vary substantially between individuals. At moderate dosages, the intended suppression of behavioural responsiveness is highly variable (Chennu et al., 2016; Bola et al., 2019), and at deep anaesthesia dosages, in rare cases (0.1-0.2%; Mashour and Avidan 2015; Sandin et al., 2000), individuals retain conscious awareness, also known as 'unintended intraoperative awareness' (Pandit et al., 2017; Sanders et al., 2017; Sandin et a., 2000; Mashour and Avidan 2015). A much higher percentage of patients presumed to be unconscious during general anaesthesia (22%; Leslie et al., 2007) may have subjective experiences, such as dreaming. The brain-bases of this considerable inter-individual effect variability remain poorly understood.

A key and mostly overlooked question is what these individual differences (Searle and Hopkins 2009; Palanca et al., 2009) can reveal about the unravelling of conscious cognition as consciousness falters during anaesthesia. Propofol is the most common anaesthetic agent in clinical interventions that require the reversible suppression of consciousness. Two recent electroencephalography (EEG) studies that measured variable behavioural responsiveness during mild and moderate propofol anaesthesia reported that the participants' varying levels of responsiveness were differentiated by alpha band connectivity during wakefulness (Chennu et al., 2016), and changing patterns of EEG signal diversity from wakefulness to moderate sedation (Bola et al., 2019). However, the brain regional- or network-bases for this substantial individual variability (Searle and Hopkins 2009; Palanca et al., 2009), and its potential link to cognitive function, remain unknown. Propofol-induced sedation produces selective metabolic impairment and reduces brain activity bilaterally in frontal and parietal associative regions (Witon et al., 2020; Boly et al., 2008; Plourde et al., 2006; Alkire 2005; Baars et al., 2003; Fiset et al., 1999; for a review see MacDonald et al., 2015; but see Pal et

al., 2020). Therefore, three brain networks with frontal and parietal lobe distribution, the dorsal attention network (DAN), executive control network (ECN), and default mode network (DMN) are primary candidate sources of individual variability under propofol sedation.

The DAN and ECN, distributed laterally across frontal and parietal lobes, are key to orchestrating stimulus-driven and goal-directed cognition. Their roles include, orienting and modulating attention to the saliency of incoming stimuli, monitoring and analysing information from the environment and integrating it with internally generated goals, as well as planning and adapting new behavioural schemas to take account of this information (Duncan 2010; Elliott 2003; Corbetta and Schulman 2002; Kroger et al., 2002; Shallice 1988). The DMN extends partially in lateral and medial frontal and parietal lobes and is thought to mediate internally-oriented cognition, e.g., autobiographical memory, imagination, and thinking about the self (Andrews-Hanna et al. 2010; Schneider et al., 2008; Buckner et al., 2008; Beer 2007; D'Argembeau et al., 2005; Wicker et al., 2003; Gusnard et al., 2001). Recent studies show that it is also involved in external environment monitoring (Spreng et al. 2014; Buckner et al. 2008; Hahn et al., 2007), including encoding of scenes, episodes or contexts (Vatansever et al., 2017), or shifts in contextually relevant information (Smith et al., 2018). Recent studies that investigate state-related manipulations (conscious vs unconscious) show that by, contrast to other brain networks, the DAN, ECN and DMN are selectively impaired during loss of consciousness, not only under anaesthesia but also during severe brain injury (Luppi et al., 2019; Naci et al., 2018). Thus, they provide strong evidence that these three networks are part of a common brain mechanism disrupted during loss of consciousness across vastly different conditions.

It is well established that the DAN/ECN and the DMN display an antagonistic relationship (Huang et al., 2020;Fox et al., 2005; Fransson et al., 2005) during spontaneous thought and goal-directed cognition. During conditions that engage external-attention, the reduction of functional activity in the DMN (Greicius et al., 2003, Raichle et al., 2001, Shulman et al. 1997), is concomitant with an increase of activity in the DAN and ECN (Seeley et al. 2007; Dosenbach et al. 2007; Fox et al., 2005; Sridharan et al. 2008). The anticorrelation between these is related to individual differences in performance variability (Kelly 2008), and directly supports sustained attention (Kucyi et al., 2020). More broadly, it has been suggested to facilitate ongoing switches between internally- and externally biased modes of attention

(Honey et al., 2017; Buckner et al., 2013) that contribute to consciousness (Carhart-Harris and Friston 2010). Conversely, this antagonistic relationship breaks down in state-related manipulations of consciousness, such as during sleep (Tagliazucchi et al., 2013), anaesthesia (Bonhomme at el., 2012; Boveroux et al., 2010), and severe brain injury (Haugg et al., 2018; Boly et al., 2009). Despite this accumulating evidence for the key and interrelated roles of the DAN, ECN, and DMN in supporting conscious cognition (Huang et al., 2020; Demertzi et al., 2013; Vanhaudenhuyse et al., 2011), and their primacy as target sites of propofol-induced sedation, their roles in individual differences under anaesthesia have not been previously investigated.

To address this gap, in two studies we tested whether variability or impairments in functional connectivity within and between the DAN, ECN, and DMN underlie individual differences in responsiveness during propofol anaesthesia. To directly investigate their individual and joint roles, in a first fMRI study we scanned healthy volunteers (N=17) during wakefulness and during the administration of propofol at dosages of 'moderate anaesthesia,' expressly aimed at engendering individual differences. Prior to the wakefulness and moderate anaesthesia scans, participants were asked to perform a verbal recall memory test that assessed basic memory function. Variability in behavioural responsiveness in each state was assessed with an auditory target detection task prior to scanning. To test whether any individual differences in responsiveness were related to differences in information processing that were invisible to the clinical sedation scale (Ramsay et al., 1974), participants were scanned during an active information processing condition comprised of a brief (5 minutes) engaging auditory narrative, and during a control condition of spontaneous thought, i.e., the resting state. Listening to plot-driven narratives is naturally engaging, requires minimal behavioural collaboration from volunteers, and therefore, is highly suitable for testing information processing independently of behavioural output or eye opening (Naci et al., 2018; 2017), which are impaired in moderate anaesthesia. In a second behavioural study, we assessed the high-level attention demands of narrative understanding in an independent behavioural group (N=25), and related them to the brain activity of participants who underwent scanning. Finally, to test whether individual differences under anaesthesia related to inherent brain features independent from the propofol sedation, we investigated the functional connectivity between and within the three networks during wakefulness, as well as grey matter volume differences across participants.

Methods

Participants

Study 1. Healthy participants for the fMRI scanning anaesthesia study (N=17; 18-40 years; 13 males) were tested at the Robarts Research Institute, Western University, in Canada. Ethical approval was obtained from the Health Sciences Research Ethics Board and Psychology Research Ethics Board of Western University. Data from the wakefulness condition was previously reported in Naci et al., 2018.

Study 2. The independent group of healthy participants (N=25; 18-40 years; 7 males) for the behavioural suspense rating study were tested at the Global Brain health Institute at Trinity College Dublin, in Ireland. Ethical approval was obtained from the School of Psychology Research Ethics Board, Trinity College Dublin.

All healthy participants were right-handed, native English speakers, and had no history of neurological disorders. Both studies were performed in accordance with the relevant guidelines and regulations set out by the research ethics boards. Informed consent was obtained for each participant prior to the experiment.

Stimuli and Design

Study 1

Behavioural testing. *Memory recall task*. The brief recall from the Mini Mental State Exam (Folstein et al., 1975) was adopted to test memory function under sedation. The researcher named three unrelated objects clearly and slowly and asked the volunteer to name each of them. The volunteer was instructed to remember the words in order to be able to repeat them in a short while. After 10 minutes, the volunteer was asked the repeat the words. Two different lists (a. Ball- Flag-Tree; b. Flower-Egg-Rope) were used to avoid familiarity effects between the wakeful and moderate anaesthesia states. Their presentation was counterbalanced across participants.

Auditory target detection task. Before the wakeful and moderate anaesthesia fMRI sessions, participants were asked to perform a computerized auditory target detection task (4 minutes), which aimed to assess individual differences during moderate anaesthesia. Participants were instructed via headphones to press a button with their index finger as soon as they heard an auditory beep and to keep their eyes on the fixation cross on the screen. The response box was tapped to the hand to ensure the participant did not lose contact during anaesthesia. The averaged reaction time (RT) for each participant was computed for further analyses.

MRI testing. Inside the MRI scanner, participants underwent two functional scans during wakefulness and moderate anaesthesia. A plot-driven audio narrative (5 minutes) was presented over MRI compatible noise cancelation headphones (Sensimetrics, S14; www.sens.com), and participants were asked to simply listen with eyes closed. The story comprised a highly engaging auditory excerpt from the movie 'Taken' depicting dramatic events, where a young girl travelling abroad without her family is kidnapped while speaking on the phone to her father. A similar eyes-closed, resting state condition (8 minutes) was also acquired in each state for comparison with the narrative condition.

Sedation Procedure. The level of sedation was measured with the Ramsay clinical sedation scale for each participant by 3 independent assessors (two anaesthesiologists and one anaesthesia nurse) in person inside the scanner room. Before entering the fMRI scanner, a 20G I.V. cannula was inserted into a vein on the dorsum of the non-dominant hand of the participants. The propofol infusion system was connected to the cannula prior to the first scanning session. No propofol was administered during the wakeful session. Participants were fully wakeful, alert and communicated appropriately (Ramsay 1) and wakefulness (eye-opening) was monitored with an infrared camera placed inside the scanner. At the commencement of the moderate anaesthesia session, 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 the sedative effect of Propofol. This infusion pump was manually adjusted to achieve the 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). In accordance with the Canadian Anaesthesia Society (CAS) guidelines, non-invasive blood pressure (NIBP), heart rate, oxygen saturation (SpO2) and end-tidal carbon dioxide (ETCO2) were monitored continuously through the use of a dedicated MR compatible anaesthesia monitor. Complete resuscitation equipment was present throughout the testing.

Propofol infusion commenced with a target effect-site concentration of 0.6 μg/ml and oxygen was titrated to maintain SpO2 above 96%. Throughout sedation, participants remained capable of spontaneous cardiovascular function and ventilation. Supplemental oxygen was administered via nasal cannulae to ensure adequate levels of oxygen at all times. If the Ramsay level was lower than 3 for moderate sedation, the concentration was slowly increased by increments of 0.3 μg/ml with repeated assessments of responsiveness between increments to obtain a Ramsay score of 3. During administration of propofol, participants generally became calm and slowed in their response to verbal communication. Once participants stopped engaging in spontaneous conversation, and speech became sluggish, they were classified as being at Ramsey level 3. Nevertheless, when asked via loud verbal communication participants agreed to perform the auditory target detection and memory recall tasks, as would be expected at Ramsey level 3. During moderate anaesthesia (Ramsey 3), the mean estimated effect-site propofol concentration was 1.99 (1.59- 2.39) μg/ml and the mean estimated plasma propofol concentration was 2.02 (1.56- 2.48) μg/ml.

Study 2

To provide a subjective measure of attention during the story, participants rated how "suspenseful" it was every 2 seconds, from 'least' (1) to 'most suspenseful' (9). Participants heard the stimulus through over-ear headphones in sound-isolated rooms at the Global Brain Health Institute at Trinity College Dublin. Laboratory computers were used to present the stimulus, cue and collect responses. The audio excerpt was divided into 156 clips, each 2 seconds long to match the repetition time (TR, 2 sec) used in independent participant group who underwent MRI scanning. Participants had up to 3 seconds to make a response, at which point the next sequential clip began immediately. At the end of experiment, participants indicated via a feedback questionnaire that the interruptions did not disrupt the coherence of the story's plot and their perception of suspense throughout.

Data Analyses

Study 1

MRI Data Acquisition. Functional images were obtained on a 3T Siemens Prisma system, with a 32-channel head coil. The high-resolution brain structural images were acquired using a T1-weighted 3D MPRAGE sequence with following parameters, voxel size: 1 x 1 x 1 mm, TA=5 minutes and 38 seconds, echo time (TE) = 4.25ms, matrix size=240x256x192, flip angle (FA) = 9 degrees. The functional echo-planar images (EPI) images were obtained with following parameters, 33 slices, voxel size: 3 x 3 x 3, inter-slice gap of 25%, repetition time (TR) = 2000ms, TE=30ms, matrix size=64x64, FA=75 degrees. The audio story and resting state had 155 and 256 scans, respectively. A volume level deemed comfortable by each individual was used for the duration of the scanning.

MRI preprocessing: 1) Functional data. Standard preprocessing procedures and data analyses were performed with SPM8 (Wellcome Institute of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and the AA pipeline software (Cusack et al., 2015). In the preprocessing pipeline, we performed slice timing correction, motion correction, registration to structural images, normalization to a template brain, and smoothing. The data were smoothed with a Gaussian smoothing kernel of 10mm FWHM (Peigneux et al. 2006). Spatial normalization was performed using SPM8's segment-and-normalize procedure, whereby the T1 structural was segmented into grey and white matter and normalized to a segmented MNI-152 template. These normalization parameters were then applied to all EPIs. The time series in each voxel was high pass-filtered with a cutoff of 1/128 Hz to remove low-frequency noise, and scaled to a grand mean of 100 across voxels and scans in each session. The preprocessed data were analyzed in using the general linear model. Prior to analyses, the first five scans of each session were discarded to achieve T1 equilibrium and to allow participants to adjust to the noise of the scanner. To avoid the formation of artificial anti-correlations (Murphy et al. 2009; Anderson et al., 2011), we performed no global signal regression. 2) Structural data. The brain structural images were processed using FreeSurfer package (https://surfer.nmr.mgh.harvard.edu/), a well-documented automated program which is widely used to perform surface-based morphometric analysis (Dale et al. 1999). The processing steps include: 1) removing the non-brain tissue; 2) transforming the skull-stripping brain volume to Talairach-like space; 3)

segmenting brain tissues to GM, WM, cerebrospinal fluid (CSF); 4) performing intensity normalization to remove the effect of bias field; 5) building a surface tessellation to generate a triangular cortical mesh consisting of about 300,000 vertices in the whole brain surface; 6) correcting topological deficits of cortical surface; and 7) deforming brain surface to generate optimized models of GM/WM and GM/CSF boundaries.

Analyses of fMRI data. To investigate whether the behavioural variability under anaesthesia related to perceptual or higher-order processing differences among participants, we performed two mixed data-driven and model-based analyses. First, we extracted the sound envelope of the auditory narrative via the Matlab *MIR*toolbox (http://www.jyu.fi/hum/laitokset/musiikki/en/research/coe/materials/mirtoolbox) and built a generalised linear model (GLM) by using statistical parametric mapping to derive auditory characteristic-related brain activation for each individual. Subsequently, the z-scored average suspense ratings of the narrative obtained by the independent group of participants in study 2 were used as a regressor in the fMRI data of individuals who underwent propofol anaesthesia in study 1, to measure the neural correlates of information processing during the narrative condition. The regressors were generated by convolving boxcar functions with the canonical hemodynamic response function. Also included in the general linear model were nuisance variables, comprising the movement parameters in the three directions of motion and three degrees of rotation, as well as the mean of each session. Fixed-effect analyses were performed in each subject, corrected for temporal auto-correlation using an AR (1)+white noise model. Linear contrasts were used to obtain subject-specific estimates for each effect of interest. Linear contrast coefficients for each participant were entered into the second level random-effects analysis. Clusters or voxels that survived at $p<0.05$ threshold, corrected for multiple comparisons with the family wise error (FWE) were considered statistically significant.

Functional connectivity (FC) within and between the DAN, ECN, and DMN was assessed by computing the Pearson correlation of the fMRI time courses between 19 regions of interests (ROIs) (from Raichle 2011) constituting these different brain networks, as identified by resting state studies (Table 1). Permutation (1000 times) tests were used to explore FC difference between conditions and were FDR corrected for multiple comparisons. All of the analyses were conducted using Fisher z-transformed correlation (Pearson *r*). Pearson correlation cannot directly imply causal relations between neural regions, but it is a simple

FC measure with minimal assumptions. It is adequate for our purpose because the time-course and spatial extent of fronto-parietal and default mode networks encompassed a vast swath of hierarchical processing cascade and, thus, many regions of cause-effect space were triggered by the stimulus. FC within and between these networks, indicated by Pearson correlation, reflected their interactions over several minutes and the resulting computations on the information content of the narrative condition, or of spontaneous thought during the resting state condition. Glass's delta was used to compute the effect size of the comparison between wakeful and moderate anaesthesia states, because of the different standard deviations of the two states, while Hedges' *g* was used to compute the effect size of the comparison between fast and slow responders because of the different sample sizes for the two groups.

Grey matter volume analyses. Grey Matter Volume (GMV) was computed as the volume of a truncated tetrahedron. The reconstructed surface was smoothed with a 10-mm full-width at half maximum (FWHM) Gaussian kernel to perform the statistics. Based on group-level comparison, we detected the clusters showing significant GWM differences at the group-level. Monte Carlo simulation cluster analysis and a cluster-wise threshold of $p < 0.05$ was adopted for multiple comparisons correction. In this way, we identified the regions with significant group differences in GMV. We then extracted averaged GMV of each significant cluster for individual participants and performed permutation tests (1000 times) to identify the group difference between fast and slow responders.

Study 2

Analyses of suspense ratings. A group-averaged set of suspense ratings were calculated by averaging participants' ratings at each time-point. To determine how similar suspense ratings were across the group, the inter-subject correlation of suspense ratings was computed as the average of the Pearson correlations of each participant's data with the mean data from the rest of the group. To compute the average correlation value, each correlation coefficient was normalized using Fisher's r-to-z transformation and the average of these values was computed and then back-transformed into a correlation coefficient.

Results

The effect of moderate anaesthesia on brain network connectivity

Initially, we investigated how moderate propofol anaesthesia perturbed the patterns of functional connectivity (FC) relative to wakefulness across all the participants (Figure 1). For the narrative condition, a 2x2 ANOVA that explored the main effects of *state* (wakefulness, moderate anaesthesia) and *network connectivity* (DMN, DAN, ECN, DMN–DAN, DMN–ECN, DAN–ECN) showed significant main effects of state ($F(1, 16) = 5.3$, $p < 0.05$), network connectivity ($F(2.9, 46.7) = 28.1$, $p < 0.0001$), and a significant interaction effect of state by network connectivity ($F(5, 80) = 8.2$, $p < 0.0001$). We investigated further this interaction effect by testing the effect of sedation state on each network connectivity. We found significantly higher DMN–DAN (permutation test, $p < 0.01$, FDR corrected), as well as DMN–ECN (permutation test, $p < 0.05$, FDR corrected) connectivity in moderate anaesthesia relative to wakefulness, during the narrative condition (Figure 1B).

For the resting state condition, a 2x2 ANOVA that explored the main effects of *state* (wakefulness, moderate anaesthesia) and *network connectivity* (DMN, DAN, ECN, DMN–DAN, DMN–ECN, DAN–ECN) showed a significant main effect of network connectivity ($F(2, 32.3) = 18.9$, $p < 0.0001$) and a significant interaction effect of state by network connectivity ($F(2.4, 38.8) = 4.3$, $p < 0.05$). However, we found no significant differences between wakefulness and moderate anaesthesia for each network connectivity (Figure 1B).

A direct comparison between the narrative and resting state conditions, with a 2x2 ANOVA [*condition* (narrative, resting state) x *network connectivity* (6 levels)] on the FC difference values (moderate anaesthesia - wakefulness), showed a significant main effect of network connectivity ($F(5, 80) = 9.9$, $p < 0.0001$), and no main effect of condition or interaction effect. Although the 2x2 ANOVA did not reveal any interactions, effect size analyses showed higher effect sizes of moderate anaesthesia in the narrative relative to the resting state condition for both DMN–DAN (Glass' Delta = 1.20 vs 0.52) and DMN–ECN (Glass' Delta = 1.02 vs 0.46). In summary, these results suggested that the antagonistic relationship between the DMN and the DAN/ECN and was reduced during moderate anaesthesia, with a stronger and significant result in the narrative condition relative to the resting state.

Figure 1. about here please

The effect of moderate anaesthesia on behavioural responsiveness

Despite the same Ramsay 3 clinical score, independently determined by three assessors, we observed significant heterogeneity in the reaction time of the auditory detection task (Figure 2). 5/17 participants were not delayed significantly relative to their non-sedated responses, 9/17 were significantly delayed and had fragmented responses (showing 2–40% missing trials), and 3/17 failed to make any responses (full omission of responses), despite agreeing to have understood the task instructions and to make responses via the button box affixed to their dominant hand. This large individual variability was at odds with the propofol infusion rates titrated for each participant based on the pharmacokinetic model adjusted for demographic variables (Marsh et al., 1991), to maintain stable target blood concentrations consistent with Ramsay 3 sedation level (Ramsay, 1974). Additionally, all participants successfully completed the brief delayed recall memory task.

To further investigate these individual differences in responsiveness, individuals were divided into two groups, fast responders (FRs; N=11), and slow responders (SRs; N=6) based on the mean split of reaction time (Figure 2). Individual responsiveness variability was not explained by demographic differences, as suggested by no differences in age (between-samples *t*-test, $t = -0.42$, $p = 0.677$) and gender (Fisher's exact test, odds ratio = 0.47, $p = 0.584$) between FRs and SRs.

Figure 2. about here please

Rather, the brain-bases of this variability may be related to three other factors. First, the individual variability could be related to underlying fine-grained perceptual and/or higher-order information processing differences between participants, which may have been invisible to the behavioural examination during the Ramsay assessment. For example, participants who made no responses during moderate anaesthesia, may have appeared to understand the task instructions based on their limited verbal responses, despite genuine lack of understanding, which may have led to failure of button-press responses. Second, independently of the extent of information processing in each individual, responsiveness

differences may be driven by connectivity alterations within and between the DAN, ECN and DMN networks, which would suggest impairments in other cognitive processes. Third, individual responsiveness differences may be related to structural brain differences, which may, in turn, manifest as differences in information processing and/or functional connectivity. In the following analyses, we explored each of these factors in turn.

Information processing and behavioural responsiveness during moderate anaesthesia

To measure information processing during the auditory narrative, we used a previously established method (Naci et al., 2018; 2017; 2014), where we demonstrated that the extent of stimulus-driven cross-subject correlation provides a measure of regional stimulus-driven information processing. During wakefulness, we observed widespread and significant ($p<0.05$; FWE cor) cross-subject correlation between healthy participants, bilaterally in sensory-driven (primary and association) auditory cortex, visual cortex, as well as higher-order frontal and parietal cortical regions (Figure 3A). By contrast, during moderate anaesthesia, significant ($p<0.05$; FWE cor) cross-subject correlation was observed only in primary and secondary auditory cortex and three small clusters (the left post central gyrus, left paracentral lobule and right precentral gyrus) of premotor and motor cortex that have been implicated in language comprehension (Hauk et al., 2004) (Figure 3B). As expected, and consistent with previous studies (Naci et al., 2018; Davis et al., 2007), these results suggested reduced information processing during moderate anaesthesia relative to wakefulness.

Figure 3. about here please

We delved deeper into these effects to investigate whether each individual's sensory-driven (auditory) perceptual processes and high-order attention processes during the story condition, related to their response times in the target detection task. First, we used SPM to model the relationship between the story's sound envelope and changes in brain activity over time. At the group level, during wakefulness, the sound envelope predicted brain activity in bilateral primary and secondary auditory cortex and right inferior frontal gyrus (Figure 3C). This

activity was dramatically reduced in moderate anaesthesia to one small cluster in left primary auditory cortex (superior temporal gyrus) that did not reach statistical significance (p=0.05 FWE cor) (Figure 3D). At the individual level, the sound envelope predicted significant activations in the auditory regions in 14/17 participants (3/17 showing subthreshold activations) during wakefulness, and in 10/17 during moderate anaesthesia. We observed no correlation between the participants' reaction times in either wakefulness or moderate anaesthesia and the extent of their individual activations in auditory regions (Figure 3 G–H).

Second, to investigate differential recruitment of high-order attention processes during the story, we used a previously established qualitative measure of the listeners' sustained attention throughout the narrative — the perception of suspense on a moment-by-moment basis (Naci et al., 2014). Beyond basic physical properties captured in the sound envelope, such as the amplitude and tone of the musical soundtrack, 'suspense,' in dramatic narratives such as the one used in this study, arises through ongoing sustained attention, as the current features of the movie (e.g., a young girl is alone in a foreign country, far away from her family) are compared to stored knowledge of the world (e.g., human traffickers pray on vulnerable targets), what has happened previously in the story (e.g., the girl's close friend has been kidnapped), and what may happen in future (e.g., she may be kidnapped).

Again, we used SPM to model the relationship between this qualitative measure of the story's ongoing high-level attention demands and changes in brain activity over time, measured in the independent group of participants, who had listened to the story without a secondary task in the fMRI scanner, during the wakeful and moderate anaesthesia states. During wakefulness, suspense ratings significantly ($p<0.05$; FWE cor) predicted activity in regions of the auditory attention network (the left superior temporal gyrus, left and right inferior frontal cortex, the inferior precentral gyrus/sulcus) (Tobyne et al., 2018; Michalka et al., 2015; Naci et al., 2013) and the salience network (the left/right anterior cingulate, insula, inferior frontal, and the thalamus) (Seeley 2019; Menon 2015), with clips rated as 'highly suspenseful' predicting stronger activity in this networks (Table 2) (Figure 3E). As expected, during moderate anaesthesia, the activation predicted by suspense ratings was reduced to one cluster extending in right superior temporal and marginal gyri (Figure 3F).

Table 2 about here please

452 In the behavioural group, the suspense ratings throughout the narrative showed a very robust
453 (r=0.90; SE=0.07)) and significant inter-subject correlation (t(24)=20.56, p=9.6e-17),
454 confirming the common understanding of the story across different individuals listening to
455 this narrative. In previous work, we have shown that a common neural code that is reliably
456 present in individual participants underlies common understanding of engaging audio-visual
457 narratives (Naci et al., 2017; 2014). Therefore, the similarity of the story's suspense ratings
458 enabled model-based predictions of the underlying brain activity that could be applied to
459 individual participants. The suspense ratings predicted significant activations in the auditory
460 attention network and salience network regions in 17/17 of participants during wakefulness
461 and 14/17 during moderate anaesthesia. We observed no correlation between the participants'
462 reaction time in wakefulness or moderate anaesthesia and the extent of their individual
463 activation in the auditory attention and salience networks regions (Figure 3 I–J).

464 In summary, these results suggested that differences in behavioural responsiveness under
465 anaesthesia, were neither driven by differences in auditory perceptual processes, nor in
466 sustained attention processes and the ability to integrate complex and dynamic information
467 that unveils over time.

468

469 *Network connectivity and behavioural responsiveness during moderate anaesthesia*

470 Rather, alterations in the connectivity within and between the DAN, ECN, and DMN during
471 moderate anaesthesia may drive these individual differences. We observed that functional
472 connectivity within the ECN was the only FC type that differentiated the two response
473 groups, with significantly higher FC for FRs relative to SRs, in the narrative condition during
474 wakefulness (permutation test, $p < 0.005$, FDR corrected) (Figure 4). No FC differences
475 between FR and SR were observed within the DAN or DMN, or between any of the three
476 network pairs.

477 Figure 4. about here please

478

479 To further investigate the within–ECN FC differences between FRs and SRs, we performed a
480 2x2x2 ANOVA that explored the main effects of *condition* (narrative, resting state), *state*

481 (wakefulness, moderate anaesthesia) and *response group* (FRs, SRs), as well as any
482 interaction among them. We found a main effect of response group (F (1,15) = 7.40, $p <$
483 0.05) that was driven by higher connectivity for FRs, and no effects on condition or state.
484 Although the 2x2x2 ANOVA did not reveal any interactions, effect size analyses showed a
485 higher difference between FRs and SRs in the narrative condition during wakefulness
486 (Hedges' g = 1.58) relative to moderate anaesthesia (Hedges' g = 1.10), and relative to the
487 resting state condition during wakefulness (Hedges' g = 0.68), and moderate anaesthesia
488 (Hedges' g = 0.96). In summary, the within–ECN functional connectivity during the narrative
489 condition in the wakeful state most strongly related to the individual differences in
490 behavioural responsiveness observed during moderate anaesthesia.

491

492 *Structural brain differences and behavioural responsiveness during moderate anaesthesia*

493 Finally, we tested whether individual differences in behavioural responsiveness were related
494 to structural brain differences, which may also underlie functional connectivity differences.
495 To this end, we performed whole-brain vertex-based comparisons of grey matter volume
496 between FRs and SRs. We found that FRs had uniformly significantly higher grey matter
497 volume relative to the SRs, in five regions bilaterally distributed: the left and right superior
498 and dorsolateral frontal cortex (L SFC, R SFC), including the presupplementary motor area
499 (pre-SMA), left and right rostral middle frontal cortex (L rMFC, R rMFC) and the right
500 precentral cortex (R Precentral) (Figure 5 and Table 3). These regions overlapped with the
501 three functional ROIs that defined the frontal nodes of the executive control network (Table
502 1). The opposite effect —higher grey matter for SR than FR—was not observed anywhere in
503 the brain. These results lend support to the functional connectivity results above, and together
504 they strongly suggest that connectivity within the ECN, and especially the frontal aspect of
505 this network, underlies individual differences in behavioural responsiveness under moderate
506 anaesthesia.

507 Figure 5. about here please

508 Table 3 about here please

This was further confirmed by a direct comparison of the FC differences between FRs and SRs in the ROIs covering the frontal (dorsal medial PFC, left and right anterior PFC) and parietal (left and right superior parietal cortex) aspects of the ECN separately. A 2x2x2 ANOVA with factors *state* (wakefulness, moderate anaesthesia), *region* (frontal ECN, parietal ECN), and *response group* (FRs, SRs) showed a main effect of region [F (1,15) = 11.791, $p < 0.01$], driven by higher connectivity in the parietal aspect of the ECN, and three-way interactions (state x region x response group) [F (1,15) = 8.358, $p < 0.05$). During wakefulness, connectivity within the frontal or the parietal aspects of the ECN, independently, could distinguish FRs and SRs (permutation test, $p < 0.05$ for frontal aspect; permutation test, $p < 0.05$ for parietal aspect, FDR corrected). By contrast, in the moderate anaesthesia, only FC in the frontal aspect could significantly distinguish the FRs and SRs (permutation test, $p < 0.05$, FDR corrected) (Figure 6).

Figure 6. about here please

522 Discussion

523 Although anaesthesia has been used for over 150 years to reversibly abolish consciousness in
524 clinical medicine, the brain-bases of its considerable inter-individual effect variability remain
525 poorly understood. To address this gap, we asked whether the connectivity within and
526 between three networks that are primary sites of propofol-induced sedation and key to
527 conscious cognition — the DAN, ECN and DMN — underlie individual responsiveness
528 differences under anaesthesia. Consistent with previous studies (Chennu et al., 2016; Bola et
529 al., 2019), we observed substantial individual differences in reaction times under moderate
530 anaesthesia. These were not related to differences in perceptual or higher-order information
531 processing. Rather, only the functional connectivity within the ECN during the wakeful
532 narrative condition differentiated the participants' responsiveness level, with significantly
533 stronger ECN connectivity in the fast, relative to slow responders. These results were further
534 supported by our finding that fast responders had significantly higher grey matter volume in
535 the frontal cortex aspect of the executive control network. Taken together, the functional and
536 structural imaging results, provided very strong evidence that individual differences in
537 responsiveness under moderate anaesthesia related to inherent differences in brain function
538 and structure within the executive control network, which can be predicted prior to sedation.

539 Consistent with previous studies, we found that the antagonistic relationship between the
540 DAN/ECN and the DMN was reduced during moderate anaesthesia (Bonhomme et al., 2012;
541 Boveroux et al., 2010), but the connectivity between the DAN/ECN and DMN, or within the
542 DMN network showed no relationship to individual responsiveness variability. In addition to
543 orchestrating internally-oriented cognition (Andrews-Hanna et al. 2010; Schneider et al.,
544 2008; Buckner et al., 2008; Beer 2007; D'Argembeau et al., 2005; Wicker et al., 2003;
545 Gusnard et al., 2001), the DMN was recently found to play a role in broad associative
546 processes (Smith et al., 2018;Vatansever et al., 2017). The absence of a relationship between
547 the DMN connectivity and responsiveness differences is fitting given that the target detection
548 task did not elicit rich episodic information or any contextual shifts. Furthermore, it suggests
549 that individual differences in responsiveness were not driven by differences in internally-
550 oriented, or self-referential cognitive processes.

551 The differential impact of moderate anaesthesia on cognitive process can be inferred in a post
552 hoc manner, based on the perceptual and cognitive processes recruited by the target detection

task and the brain networks and regions that showed functional and/or structural differences between the participants. The task involved a hierarchy of perceptual and cognitive processes. These included (a) auditory perception, (b) understanding of linguistic instruction, (c) short-term memory to remember instructions for the duration of the experiment, (d) attention to auditory stimuli, (e) attention to intention to make a response, (f) cognitive control over other, competing and distracting mental processes, and the (g) execution of a motor response, when prompted by the auditory stimuli. The Ramsay clinical assessment determined similar basic language communication (b), and we found short-term memory function (c) across participants during moderate anaesthesia. Furthermore, our results showed no relationship between behavioural responsiveness and sensory/auditory (a), or higher-order, including linguistic information-processing that relied on sustained attention (b, d), across participants. Therefore, differences in responsiveness were likely underpinned by differences in complex mental faculties, such as attention to intention, cognitive control and action execution.

Our functional connectivity results demonstrated that FC within the ECN differentiated the participants' level of responsiveness, suggesting that moderate anaesthesia impacts processes of goal and action execution subserved by the ECN (Marek and Dosenbach 2018; Dosenbach et al., 2007; Ernst and Paulus 2005). Furthermore, our structural imaging results demonstrated that grey matter volume differences in the frontal cortex aspect of the ECN, including the dorsolateral prefrontal cortex (DLPFC) and pre-supplementary motor area (pre-SMA), underscore individual responsiveness differences. In addition to their role in action selection and execution (Lee et al., 1999; Boly et al., 2007), the DLPFC and pre-SMA represent higher-order attention, i.e., attention to intention. Lau et al (2004) investigated the brain regions that were preferentially involved in attending to the intention to move, relative to the actual movement, and found that brain activity in pre-SMA, as well as its functional connectivity with right DPFC represented the intention to move. The pre-SMA has also been implicated in sustained cognitive control (Nachev et al., 2005), another process that is key to successful task performance. In summary, a post-hoc interpretation of our findings would be that moderate anaesthesia impacts attention to intention, sustained cognitive control, and action execution, and that individuals with smaller grey matter volume in frontal regions and weaker functional connectivity within the ECN may have a vulnerability for stronger suppression of behavioural responsiveness than those with higher values for these features.

585 As the suppression of behavioural responsiveness is one of the key aims of anaesthesia, the
586 converse finding was also highly relevant. Surprisingly, we found that 30% of participants
587 showed no delay in reaction times under moderate anaesthesia relative to wakefulness, and
588 critically, these exhibited inherent brain differences to participants who were significantly
589 delayed. This result is highly relevant to the prediction of responsiveness variability under
590 anaesthesia (Chennu et al., 2016; Palanca et al 2009) and monitoring depth-of-anaesthesia for
591 the detection of unintended intraoperative awareness. Although rare (0.1-0.2%, Mashour and
592 Avidan 2015; Sandin et al., 2000), unintended awareness can be very traumatic and lead to
593 negative long-term health outcomes, such as post-traumatic stress disorder (up to 70%), as
594 well as clinical depression or phobias (Pandit et al., 2017; 2014; Mashour and Avidan 2015).
595 Given its rarity, unintended intraoperative awareness does not lend itself to direct
596 investigation in the relatively small groups of typical research studies with vulnerable
597 populations, including the present study, where individuals were deeply anaesthetized
598 without intubation in a research MRI setting.

599 Our results suggest that individuals with larger grey matter volume in frontal regions and
600 stronger functional connectivity within the ECN may require higher doses of propofol to
601 become non-responsive, to the same extent as individuals with smaller grey matter volume
602 and weaker connectivity in these regions. If replicated in a clinical context, these findings
603 will provide novel markers that may help to improve the accuracy of awareness monitoring
604 during clinical anaesthesia. It is worth noting that propofol was used here due to its wide
605 prominence in clinical interventions, and future studies that employ the same paradigm across
606 different agents will determine whether the brain-behaviour relationships we report here
607 generalize to other anaesthetic agents.

608 Finally, we observed higher power for detecting individual responsiveness differences under
609 anaesthesia from ECN functional connectivity in the wakeful narrative condition, than in the
610 resting state. This may be due to higher signal to noise during the narrative condition.
611 Previous studies have shown that the active attention engagement during well-crafted
612 narratives leads to reduced movement (Centeno et al., 2016) and less sleep in scanner
613 (Centeno et al., 2016, Vanderwal et al., 2015), resulting in higher signal-to-noise relative to
614 resting state (rs) fMRI (Wang et al., 2017). Moreover, it may be due to higher power to detect
615 functional roles of brain networks during naturalistic stimuli relative to rsfMRI. Rs fMRI is
616 entirely unconstrained, and thus it is difficult to separate signal due to cognitive processes

from extraneous sources, including motion, cardiac and respiratory physiological noise, arterial CO2 concentration, blood pressure, and vasomotion (Murphy et al., 2013; Birn et al., 2006). By contrast, as we have previously established, naturalistic narratives drive diverging responses across brain networks, highlighting their functionally distinct roles, and thus may be more sensitive for investigating how their differing cognitive roles are impacted by anaesthesia than rsfMRI (Naci et al., 2018; Haugg et al., 2018; Naci et al., 2014). Our results are consistent with a growing recognition of the importance of naturalistic stimuli for studying cognitive processes and understanding the neural basis of real-world functioning (Sonkusare et al., 2019).

Figures and Legends

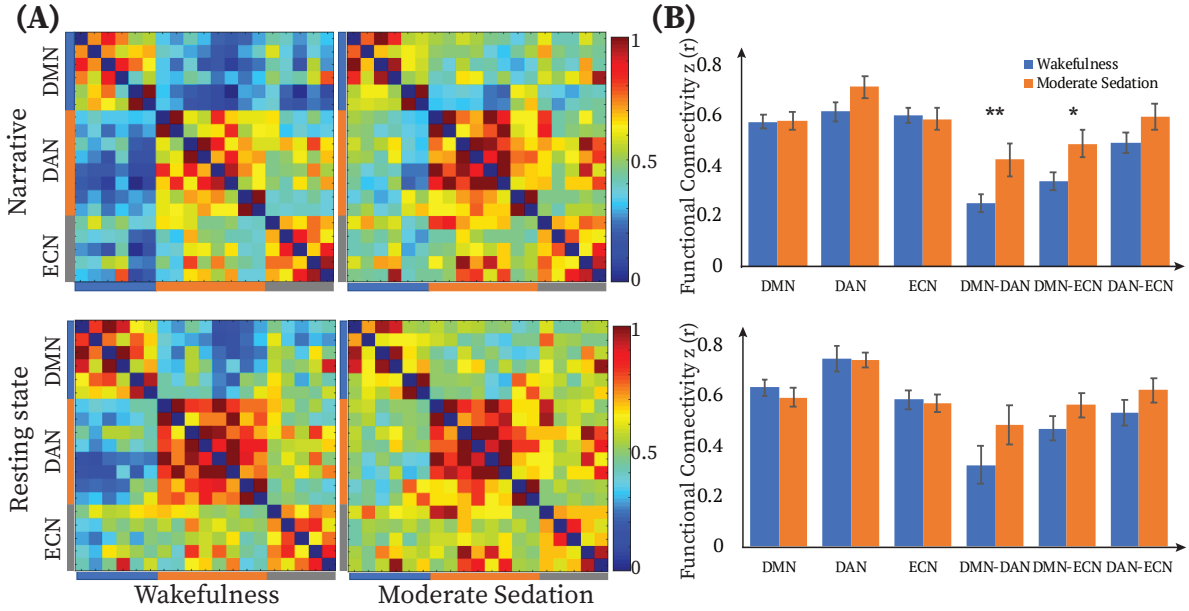


Figure 1. Functional connectivity (FC) in wakeful and moderate anaesthesia states for the narrative and resting state conditions. (A) Group-averaged FC connectivity matrices during wakeful and moderate anaesthesia states in the narrative and resting state conditions across all participants. The color bar indicates connectivity (measured as z-transformed Pearson correlation; low-high, blue-red). Each cell in the FC matrix represents FC between each node (brain region) of the three networks. (B) Comparisons of FC averaged across all nodes for each network, within and between the three brain networks, during the wakeful and moderate anaesthesia states, in the narrative and resting state conditions separately. FDR correction was applied for multiple comparison comparisons. Abbreviations: DMN, default mode network; DAN, dorsal attention network; ECN, executive control network.

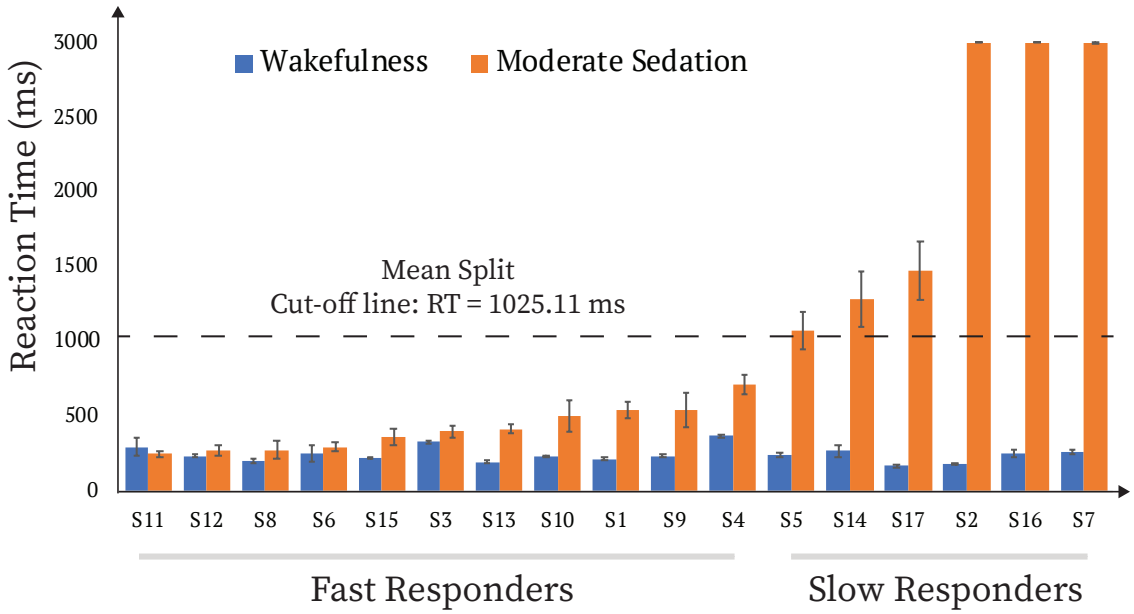


Figure 2. Reaction time during an auditory target detection task in the wakeful and moderate sedation states. Participants were divided into two groups by applying mean split method. Blue (orange) bars represent reaction time for each individual during wakeful (moderate) sedated state. Horizontal axis represents each individual (S1-S17=Subject1-Subject17) and vertical axis represents averaged reaction time across 50 trails.

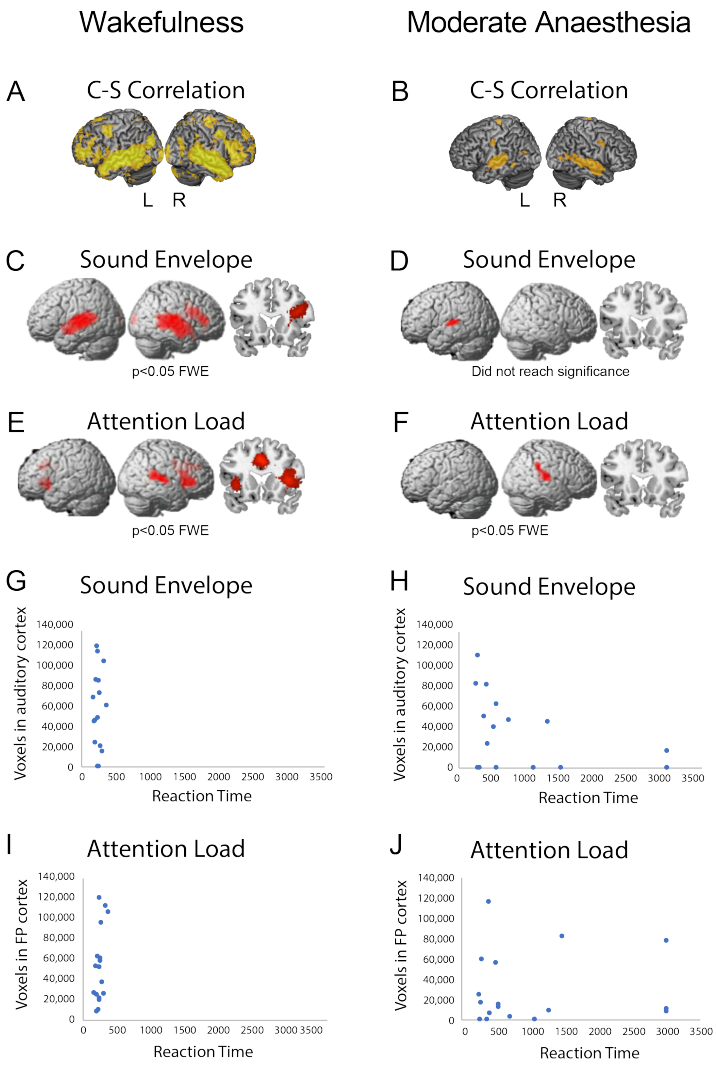


Figure 3. Perceptual and higher-order information processing during the audio story. (a) During wakefulness, the audio story elicited significant ($p<0.05$; FWE cor) inter-subject correlation across the brain, including frontal and parietal cortex, thought to support high-level information integration over time.(b) During moderate anaesthesia, significant ($p<0.05$; FWE cor) inter-subject correlation was limited to the primary and secondary auditory cortex and three small clusters in regions of premotor and motor cortex that are involved in language comprehension. (c)/(d) Clusters predicted by the sound envelope of the audio story in the (c) primary and secondary auditory cortex and left inferior frontal gyrus during wakefulness, and (d) left primary auditory cortex in moderate anaesthesia, that did not reach statistical significance ($p=0.05$ FWE). (e)/(f) Clusters predicted by the suspense ratings of the audio story in regions of the auditory attention network and salience network during wakefulness

and moderate anaesthesia. (G)/(H) The sound envelope predicted significant activations in the auditory regions in 14/17 and 10/17 of participants during the wakefulness and moderate anaesthesia states, respectively. (I)/(J) The suspense ratings predicted significant activations in the auditory regions in 17/17 and 14/17 of participants during the wakefulness and moderate anaesthesia states, respectively. (G)–(J) There was no correlation between the perceptual or higher-order information processing during the narrative and reaction times during the target detection task, either in wakefulness (G)/(H) or in moderate anaesthesia (H)/(J).

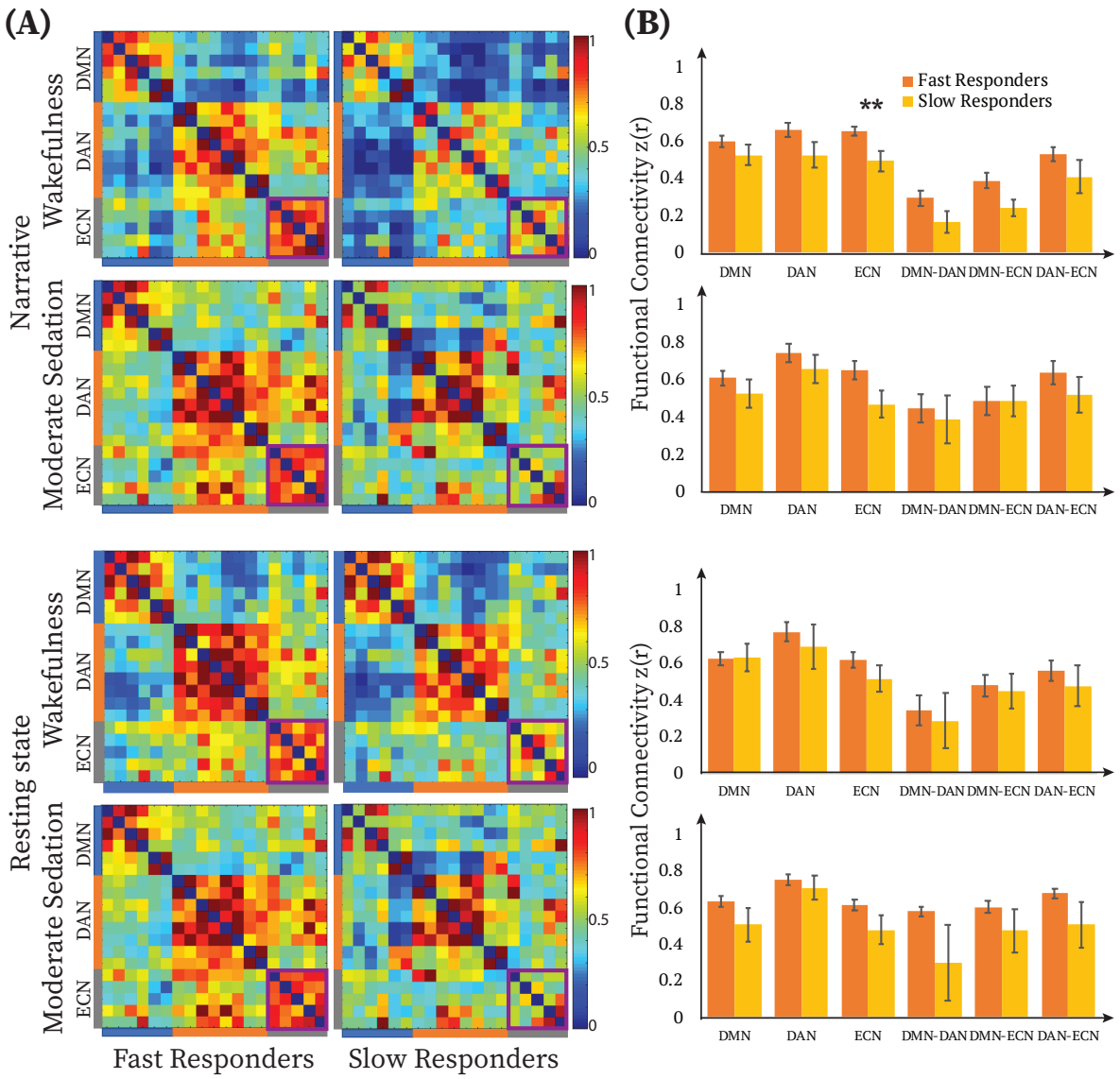
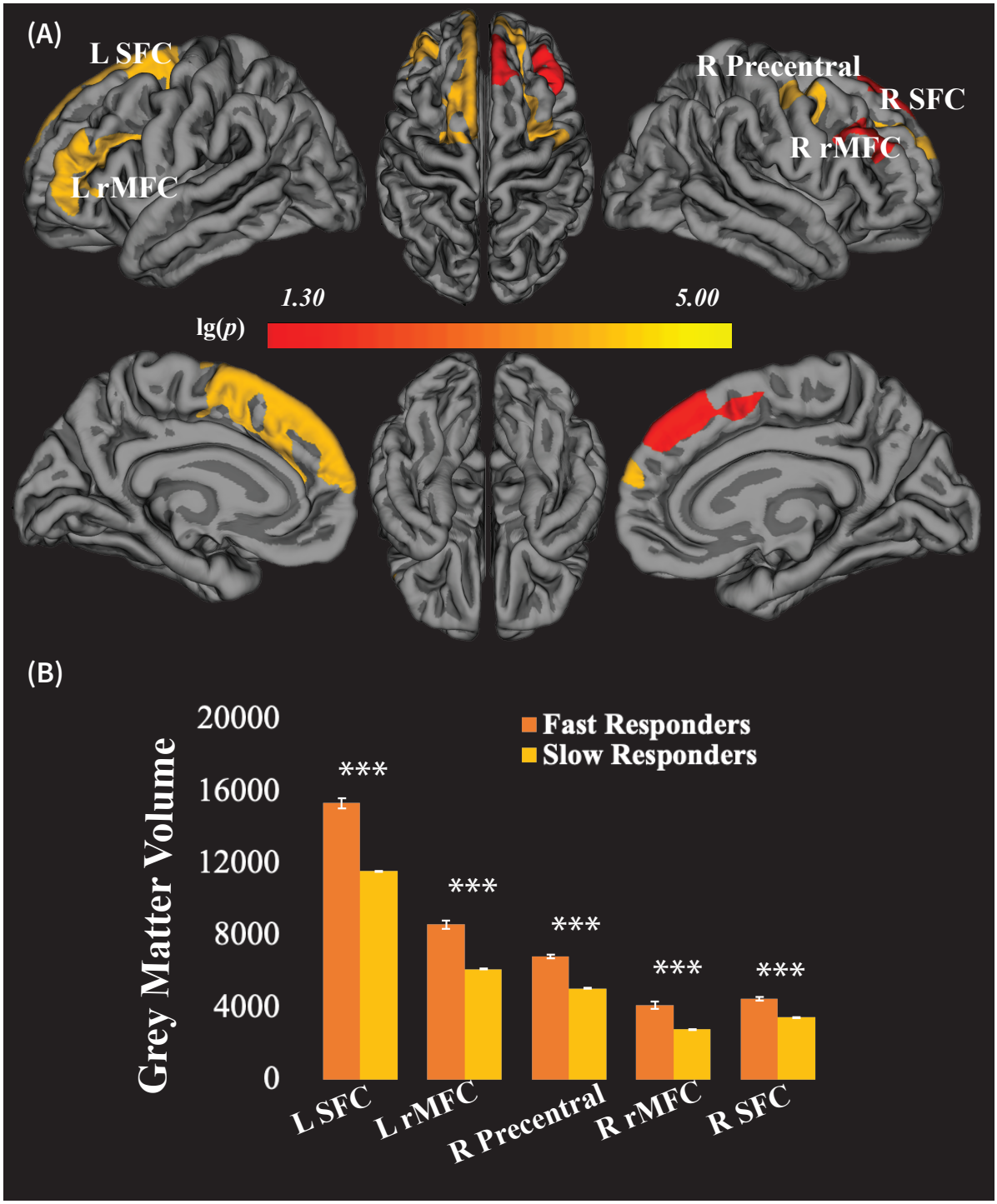


Figure 4. Functional connectivity differences between fast and slow responders. (A) FC maps for fast and slow responders during wakeful and moderate anaesthesia states in narrative and resting state conditions separately. Color bar indicates connectivity (z-transformed Pearson correlation; low-high: blue-red). Each cell in the FC map represents FC between each node (brain region) of the three networks. FC within-ECN is highlighted by the magenta square box in each FC map. (B) Comparisons of averaged FC within and between the three brain networks, between fast and slow responders for each condition and state separately. FDR correction was applied for multiple comparisons. Abbreviations: DMN, default mode network; DAN, dorsal attention network; ECN, executive control network.



683

684 **Figure 5**. Vertex-wise analysis of grey matter volume between fast and slow responders. (A)
685 Five regions showed significant between-group difference in grey matter volume (GMV, $p <$
686 0.05, Monte Carlo simulation corrected). Color bar indicates the p-value (-lg(p)). (B) Group
687 comparisons of averaged GMV for each of the five clusters between fast and slow
688 responders. Abbreviations: L SFC, left superior frontal cortex; R SFC, right superior frontal
689 cortex; L rMFC, left rostral middle frontal cortex; R rMFC, right rostral middle frontal
690 cortex. R Precentral, right precentral.

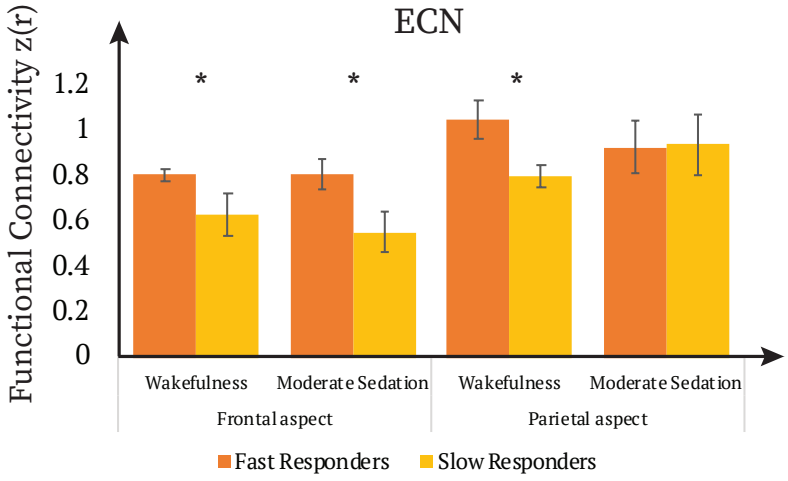


Figure 6. Differences of functional connectivity in frontal and parietal aspects of ECN between fast and slow responders in both wakeful and moderate anaesthesia states in narrative condition. Abbreviations: ECN, executive control network.

Table 1. Overview of selected regions of interests for three functional networks.

Network/Region	ROI	MNI coordinates		
		x	y	z
Default Mode Network	Posterior cingulate/precuneus	0	-52	27
	Medial prefrontal	-1	54	27
	Left lateral parietal	-46	-66	30
	Right lateral parietal	49	-63	33
	Left inferior temporal	-61	-24	-9
	Right inferior temporal	58	-24	-9
Dorsal Attention Network	Left frontal eye field	-29	-9	54
	Right frontal eye field	29	-9	54
	Left posterior IPS	-26	-66	48
	Right posterior IPS	26	-66	48
	Left anterior IPS	-44	-39	45
	Right anterior IPS	41	-39	45
	Left MT	-50	-66	-6
	Right MT	53	-63	-6
Executive Control Network	Dorsal medial PFC	0	24	46
	Left anterior PFC	-44	45	0
	Right anterior PFC	44	45	0
	Left superior parietal	-50	-51	45
	Right superior parietal	50	-51	45

Abbreviations: IPS: Intraparietal sulcus, MT: Middle temporal area, PFC: Prefrontal cortex

Table 2. Coordinates for activation cluster produced by the story's suspense ratings.

Cluster Index	**Cluster Peak Location**	**Peak Talairach coordinates** x	y	z	**Cluster-wise p-value**
1	Cingulate Sulcus	-2	20	36	<0.000
2	Right Superior Temporal Gyrus	58	-36	14	<0.000
3	Right Anterior Insular Gyrus	40	24	8	<0.000
4	Posterior Cingulate Gyrus	14	-44	14	<0.000
5	Left Anterior Insular Gyrus	-36	14	-8	<0.000
6	Thalamus	4	-20	10	<0.005

704 Table 3. Regions showing significant grey matter volume difference between slow
705 responders and fast responders

Index	Peak location	Vertex number	Size (mm2)	Peak Talairach coordinates			Cluster-wise
				x	y	z	
1	L_SFC	6163	3338.75	-6.70	29.30	48.20	1.00E-04
2	L rMFC	3048	1954.78	-38.20	25.40	22.00	1.00E-04
3	R Precentral	3257	1830.76	37.70	-1.90	40.10	1.00E-04
4	R rMFC	1592	927.63	37.80	26.80	28.50	0.0256
5	R SFC	1718	904.29	7.00	46.80	34.60	0.0304

706 Notes: Peak coordinates were presented in the Talairach-like space. Abbreviations: L SFC,
707 left superior frontal cortex; R SFC, right superior frontal cortex; L rMFC, left rostral middle
708 frontal cortex; R rMFC, right rostral middle frontal cortex. R Precentral, right precentral.

709

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Conflict of Interest

The authors declare no conflict of interest.

Author contributions

Study Conceptualization, L.N., N.T.; Data Acquisition, L.N. Methodology, R.C., F.D., L.N.; Formal Analyses, F.D., N.T.; Writing, F.D., L.N.; Funding and resource acquisition, A.M.O., L.N. Project administration, L.N.; Supervision, L.N.

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