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Exploratory Report

fMRI lag structure during waking up from early sleep stages

Santiago Alcaide [a], Jacobo Sitt [b,c], Tomoyasu Horikawa [d], Alvaro Romano [a], Ana Carolina Maldonado [e], Agustín Ibanez [f,g,h,i], Mariano Sigman [j,k], Yukiyasu Kamitani [d,l] and Pablo Barttfeld [a,*]

[a] Cognitive Science Group, Instituto de Investigaciones Psicológicas, Facultad de Psicología Universidad Nacional de Córdoba – CONICET, Argentina
[b] INSERM, U 1127, F-75013 Paris, France
[c] Institut du Cerveau et de la Moelle Epinière, Hôpital Pitié-Salpêtrière, 75013 Paris, France
[d] Computational Neuroscience Laboratories, Advanced Telecommunications Research Institute International (ATR), Kyoto, Japan
[e] Facultad de Ciencias Exactas, Físicas y Naturales, Universidad de Córdoba, CIEM-CONICET, Spain
[f] Latin American Brain Health (BrainLat), Universidad Adolfo Ibáñez, Santiago, Chile
[g] National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina
[h] Cognitive Neuroscience Center (CNC), Universidad de San Andrés, Argentina
[i] Global Brain Health Institute (GBHI), University of California San Francisco (UCSF), USA
[j] Laboratorio de Neurociencia, Universidad Torcuato Di Tella, Buenos Aires, Argentina
[k] Facultad de Lenguas y Educación, Universidad Nebrija, Madrid, Spain
[l] Graduate School of Informatics, Kyoto University, Kyoto, Japan

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ABSTRACT

The brain mechanisms by which we transition from sleep to a conscious state remain largely unknown in humans, partly because of methodological challenges. Here we study a pre-existing dataset of waking up participants originally designed for a study of dreaming (Horikawa, Tamaki, Miyawaki, & Kamitani, 2013) and suggest that suddenly awakening from early sleep stages results from a two-stage process that involves a sequence of cortical and subcortical brain activity. First, subcortical and sensorimotor structures seem to be recruited before most cortical regions, followed by fast, ignition-like whole-brain activation—with frontal regions engaging a little after the rest of the brain. Second, a comparably slower and possibly mirror-reversed stage might take place, with cortical regions activating before subcortical structures and the cerebellum. This pattern of activation points to a key role of subcortical structures for the initiation and maintenance of conscious states.

* *Corresponding author*. Cognitive Science Group, Instituto de Investigaciones Psicológicas, Facultad de Psicología Universidad Nacional de Córdoba – CONICET, Argentina.
E-mail address: pablob@conicet.gov.ar (P. Barttfeld).
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1. Introduction

Understanding how the human brain generates and reversibly loses consciousness remains one of the biggest challenges in modern neuroscience. Every day, we transition between states of consciousness, including the sleep–wake cycle (Chow et al., 2013; Siclari et al., 2017; Tagliazucchi et al., 2013; Tagliazucchi & Laufs, 2014; Tagliazucchi & van Someren, 2017). While some transitions between these states have been extensively studied, others remain almost unexplored, mostly due to methodological challenges.

The most widely studied transition is sleep-related loss of consciousness (Ogilvie, 2001; Saper, Fuller, Pedersen, Lu, & Scammell, 2010; Stevner et al., 2019)—a process typically occurring over seconds to minutes in a series of well-known sequential stages, each involving specific behavioral (Bareham, Manly, Pustovaya, Scott, & Bekinschtein, 2014; Goupil & Bekinschtein, 2012), and neural (Comsa, Bekinschtein, & Chennu, 2019; Jagannathan et al., 2018; Stevner et al., 2019; Wu et al., 2012) patterns. Though synchronized in vigilance states, at sleep onset, the thalamus and the cortex become functionally de-coupled as the former deactivates first (Magnin et al., 2010). In fact, the amount of cortico-thalamic connectivity indexes an individual's level of arousal (Barttfeld et al., 2015; Schroter et al., 2012). Substantial research has also addressed the transition from rapid eye movement (REM) sleep to non-REM (NREM), consisting in a ≤20-s state (Gottesmann, 1973) with large-amplitude sleep spindles in the electroencephalographic (EEG) signal. During a night's sleep, alternations between NREM and REM states occur every 60–90 min (Carley & Farabi, 2016; Ibanez, Silva, & Cauli, 2018; Saper et al., 2010).

In marked contrast to falling asleep, the process of waking up remains relatively less explored. Single-unit recording in mice (Takahashi, Kayama, Lin, & Sakai, 2010) showed that locus coeruleus and centromedial thalamus neurons—part of the wake-promoting subcortical networks (Saper et al., 2010)—phasically promote fast NREM–wake transitions. In humans, research on this process has focused on the states before and—especially—after the actual waking up event (i.e., wakefulness *vs* sleep/sedation resting states). The first minutes after awakening are typically marked by reduced vigilance, confusion, and diminished performance, a state termed sleep inertia (Marzano, Ferrara, Moroni, & De Gennaro, 2011; Trotti, 2017; Tsai et al., 2014; Vallat, Meunier, Nicolas, & Ruby, 2019). PET signal comparisons (Balkin et al., 2002) showed that cerebral blood flow during sleep inertia is most rapidly re-established in the brainstem and the thalamus, followed by anterior cortical regions, highlighting their role in the re-establishment of conscious awareness. Sleep inertia is also characterized by a loss of negative correlation between task-positive (dorsal attention, salience, sensorimotor) and task-negative (default mode) networks (Marzano et al., 2011). A similar scenario is observed after deep sedation (Barttfeld et al., 2015; Nir et al., 2019), as the thalamus becomes disconnected from the frontal cortex, and more connected to the temporal and occipital cortices. Also, the process of regaining consciousness is mediated by discrete ordered states, leading to full reestablishment (Hudson, Calderon, Pfaff, & Proekt, 2014).

The above mentioned studies focused on slow consciousness recovery. However, waking up can occur much faster: awakening is the only transition that can be triggered by an external stimulus, as explained by theories of global brain networks (Deco et al., 2019). This makes sense from an evolutionary perspective, since the capacity to quickly reconnect with the external world and respond to environmental stimuli should be a positively selected trait. This sudden transition remains unexplored. Here, we zoom into the actual and sudden waking up from early sleep stages due to external stimulation. To this end, we leveraged a unique, previously reported fMRI dataset (Horikawa & Kamitani, 2017; Horikawa, Tamaki, Miyawaki, & Kamitani, 2013) comprising three participants who were repeatedly awoken from early sleep stages by auditory stimulation (Fig. 1). Immediately after waking up, participants were asked to report their dreams –since the original study was design to decode neural correlates of dreaming- and remained inside the scanner until falling asleep again. The process was repeated several times per session. Polysomnography was simultaneously performed. This unique experimental design offers the opportunity of exploring the brain correlates of sudden awakenings from early sleeping stages.

2. General methods

2.1. Dataset

We used a dataset from previous fMRI sleep research (Horikawa & Kamitani, 2017; Horikawa et al., 2013). Potential participants underwent an interview about their sleeping and lifestyle habits, and three healthy candidates (all males, 27–39 years) were enrolled. They had no physical or psychiatric diseases, were receiving no medical treatment, were nonsmokers and nondrinkers, and had good sleeping habits. After giving written consent, they completed a two-day adaptation protocol in a mock scanner. Afterwards, the actual fMRI sleep experiments were conducted from 1:00 pm to 5:30 pm, and participants were asked to sleep if they could, without forcing themselves to. After falling asleep, participants were woken up at Hori stages 5 or 6 of the Hori's nine-stage EEG system (Hori, Hayashi, & Morikawa, 1994) by being called their name. Then, participants were asked to report their dream, if any, and remained inside the scanner until falling asleep again. This sequence was repeated several times per session (i.e., multiple awakenings per session). Each participants underwent several sessions until the total awakenings with visual dream reports reached at least 200 (resulting in 26, 14, and 15 sessions, respectively). During the whole scanning session, participants were asked to press a button when they heard a sound (200 Hz tone, 500 msec duration, 12–18 sec inter-stimulus intervals) to behaviorally monitor whether they had fallen asleep. The intensity of the sound was adjusted in every session to assure participants could clearly hear it, without disrupting their sleep. During these sessions, fMRI data were collected using a 3.0 T scanner (TR, 3,000 msec; TE, 30 msec; flip angle, 80 deg; Field of view (FOV), 192 × 192 mm; voxel size, 3 × 3 × 3 mm; slice gap,

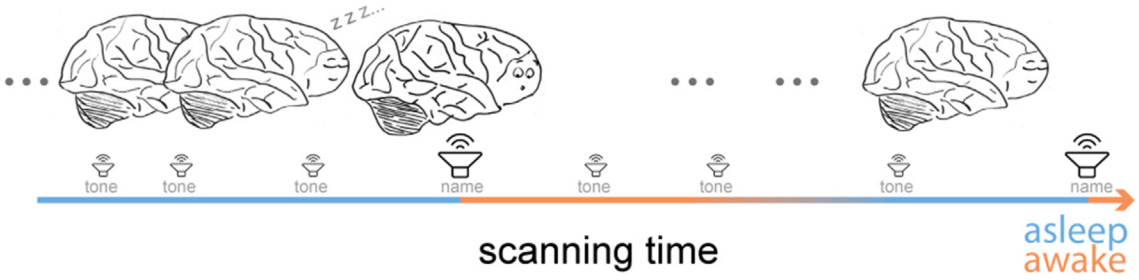

Fig. 1 – Task design. Three participants completed 55 scanning sessions. Within each session, they were repeatedly awoken from early sleep stages—upon being called by their name—, and reported what they have dreamt. To confirm they were awake, participants had to press a button every 15 sec on average after hearing a 200 Hz tone.

0 mm; number of slices, 50). T1-weighted magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) images were also acquired (TR, 2,250 msec; TE, 3.06 msec; TI, 900 msec; flip angle, 9 deg, FOV, 256 × 256 mm; voxel size, 1.0 × 1.0 × 1.0 mm).

To evaluate the sleep–wake state of the participants, polysomnography—including EEG signals from 31 scalp sites referenced to FCz (5000 Hz sampling rate, BrainVision Recorder)—were recorded along with fMRI. The examiner monitored EEG traces in real time, and channels O1 and O2 were used to establish the state of the participants. After the experiments, EEG recordings were cleaned from artifacts using the FMRIB plug-in for EEGLAB, downsampled to 500 Hz, and filtered to be used in sleep stage scoring based on the Rechtschaffen and Kales system (Rechtschaffen and Kales, 1968) that have a clear correspondence with Hori stages—awake, stage 1 and stage 2 in Rechtschaffen and Kales scale correspond to stages 1–2, stages 3–8 and stage 9 in Hori scale, respectively.

Sample size for our study was determined by the data available for reanalysis. We report all data exclusions (if any) for the reanalysis, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to reanalysis, and all measurements subjected to reanalysis.

2.2. *fMRI preprocessing and analysis*

Functional data were preprocessed using statistical parametric mapping software (SPM12; http://fil.ion.ucl.ac.uk/spm). The first fourvolumes of each run were discarded to allow for longitudinal relaxation time equilibration. Echo-planar imaging (EPI) images from all sessions were slice-time corrected. Images were already aligned to the first volume of the first session of scanning to correct for head movement between scans. Normalization parameters between the co-registered T1 and the standard MNI T1 template were then calculated, and applied to the anatomy and all EPI volumes. Data were then smoothed using an 8 mm full-width-at-half-maximum isotropic Gaussian kernel to accommodate for inter-participant differences in anatomy. For the time series analyses we removed, using REST toolbox v1.8 (Song et al., 2011), the movement parameters resulting from rigid body correction for head motion, the cerebral spinal fluid, white matter signals. We also detrended the data to rule out any confounding effect due to physiological (e.g., respiratory and cardiac) or scanning variables.

3. Analyses and results

3.1. *GLM model shows gradual network activity during waking up from early sleep stages*

3.1.1. *Analysis*

Firstly, we wanted to identify the brain regions involved in the process of waking up from early sleep stages. To this end, we conducted a general linear model using SPM software. We modeled the waking up process as a discrete event at the time participants were woken up. We defined as event regressors all waking up events (event duration of 2 sec). We contrasted events of waking-up from sleep after name-calling to events of not waking-up following control sounds. In the original experiment the control tones were delivered to identify when participants were asleep (i.e., when they did not respond to the tone). The control tones were delivered throughout the experimental session. Many tones went unresponded, either because the participants were asleep but also because participantes were allowed not to respond while verbally reporting their dream content – the times after waking up in which the participant reported what (or if) they had visual imagery during sleeping. In fact, of all the unresponded sound events, only a small proportion (between 6 and 36%) occurred during sleep. For this reason we decided to exclude all unresponded tones delivered while participants were awake. We only included in our contrast unresponded tones delivered when participants were in EEG stages 1 and 2. We included all sessions with at least 5 unreponded tones during EEG stages 1 and 2. This leave us with 26, 6 and 10 sessions per participant, respectively. This contrast controls for the baseline state (sleep) and the occurrence of a sound. We modeled the time participants remained asleep or awake as blocks of variable duration. We also included the individual movement parameters obtained from realignment as multiple regressors of no interest. We excluded from this analysis 2 sessions of participant 3 due to lack of information regarding the sound delivery and responses. As this experiment included only 3 participants, we report results for each participant separately. We ran one General linear model (GLM) model per session and computed the contrast of interest within the first level model. We then performed a *t*-test for each participant across sessions, setting a *p*-value threshold of .001 uncorrected, for display of the size effect.

3.1.2. *Findings*

We observed that an extended network of cortical and subcortical regions activates during waking up from early sleep stages (Fig. 2a). This network includes central nodes such as bilateral thalamus, bilateral insula, bilateral putamen, anterior and mid cingulate, cerebellum, temporal superior, bilateral parietal inferior, precuneus and occipital cortices (see Tables S1–3 for a list of regions and coordinates for all participants). Results varied across participants, but overlap was considerable (Fig. 2b), including thalamus, cerebellum, bilaterial parietal inferior cortex, right frontal mid cortex, precuneus and anterior and mid cingulum. Deactivations due to waking up were also observed, bilaterally in the insula (participant 1) and the cingulate gyrus (participant 3) (Tables S1–3).

The GLM model provides information regarding the regions involved in the process of waking up, but does not shed light on the dynamics of their activation. As a first step into the exploration of this dynamic, we visualized the raw BOLD signal change at the time of waking up events. We extracted the time courses of a set of 264, 5 mm ROIs grouped into 13 functional networks (Power et al., 2011), and locked the BOLD time series to the waking up event, both averaging all participants (Fig. 3a) and for individual participants (Fig. 3c). We also time-locked to the waking up the time series of all brain voxels to obtain sagittal and axial views of the brain (Fig. 3a). Renders showing representative moments of the time course were done using Pyanatomist (http://brainvisa.info/pyanatomist-4.6/sphinx/index.html) and custom software. As expected because of the nature of the analysis, the time course before waking up is a flat baseline BOLD signal (Fig. 3a and Video S1). Sharply locked to the waking up event there is a rapid increment in BOLD signal in the form of a burst-like activity that rapidly decays. This rapid activation is followed by a more prolonged wave restricted to bilateral thalamus (Fig. 3b), suggesting that a two-component process is taking place. The first component is characterized by a rapid increase in the BOLD signal starting at the auditory and subcortical regions, and followed by a burst of activity of the whole cortex that rapidly decreases (with frontal regions activating a little later). In a second phase, there is a sustained activity in thalamic regions (specifically, ROIs at [−2, −16, 13] and [−10, −21, 8]). When exploring this pattern at the

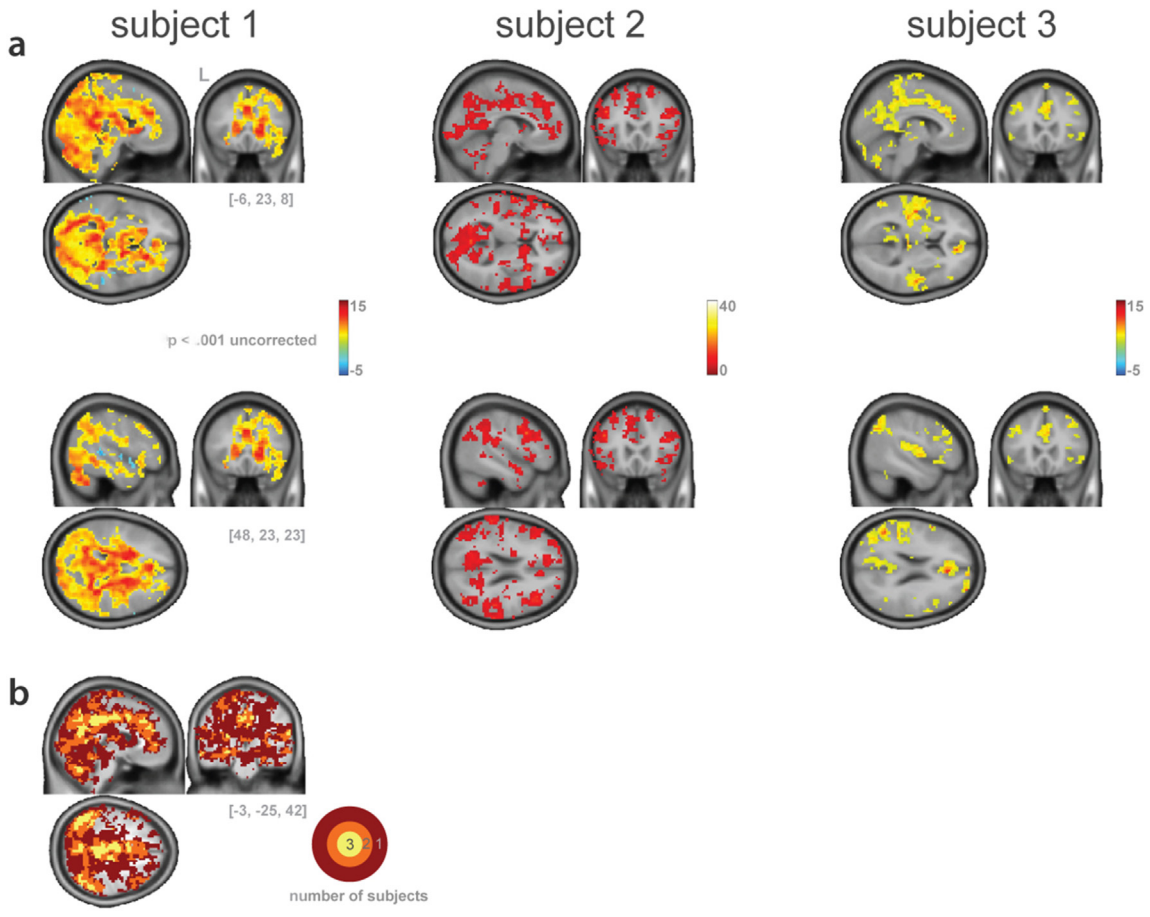

Fig. 2 – Brain regions involved in the process of waking up from early sleep stages. A\a) Intra-participant *t*-test displaying brain regions associated with waking up from early sleep stages. We contrasted events of waking up from early sleep stages due to name calling sound with events not waking up from sleep after a sound (unresponded tones) ($p < .001$, uncorrected). Significant clusters include bilateral thalamus, bilateral insula, bilateral putamen, anterior and posterior cingulate, and cerebellum. Planes chosen for display were the most illustrative. See Table S1–3 for a full description of the significant clusters. b) Overlapping clusters across participants. Color codes the number of participants included in the overlap.

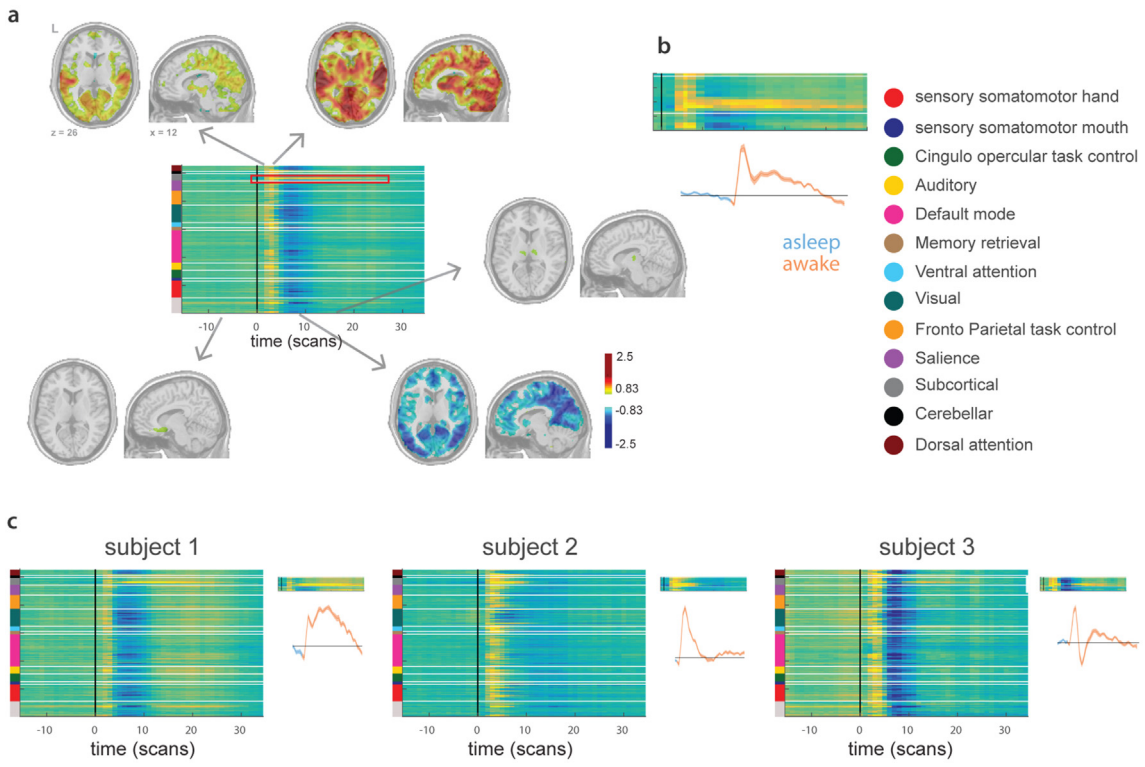

Fig. 3 – The time course of waking up from early sleep stages. a) Time series locked to the event of waking up from early sleep stages for 264 ROIs grouped into 13 functional networks. Sagittal and axial brain renders are shown at particular times. We observe a two-component process of waking up. The first component is characterized by a rapid increment in BOLD signal starting at auditory cortices and subcortical regions, followed by a burst of activity in the whole cortex that rapidly decreases. The second phase (starting 9 scans after the waking up event) includes sustained activity in the thalamus. Inserts show sagittal and axial brain BOLD signal at particular times. We zoom in the matrix to focus on the late activation of two thalamic ROIs, framed in red in panel A (b) as well as their time course that display two clear peaks. c) Same analysis for each participant. While participants 1 and 3 display a pattern similar to the average, participant 2 does not have a clear second component in thalamic regions.

individual level, however, this image seems more complex (Fig. 3c). While participants 1 and 3 show the described pattern, participant 2 does not show a clear second component, and the first component at the thalamic ROIs has a longer duration than for the other participants (Fig. 3c, center).

Supplementary video related to this article can be found at doi:10.1016/j.cortex.2021.06.005

3.2. *Lag structure suggests waking up from early sleep stages is a two-component process*

3.2.1. *Analysis*

We sought to explore the temporal pattern emerging from Fig. 3 quantitatively using the lag structure analysis (Mitra, Snyder, Hacker, & Raichle, 2014; Mitra, Snyder, Tagliazucchi, Laufs, & Raichle, 2015). This method is specifically conceived to quantify the temporal delay between time series from different brain structures, making it well suited to recover the voxel specific time delays after the waking up event. For this we adapted a published method (Mitra et al., 2014, 2015) to the time-locked structure of our study, and estimated the time lag between voxel pairs across the brain, independently for the two components previously observed (Fig. 4a and b). In our adaptation, the method was run on time-locked averaged time-series, because, unlike Mitra et al., we were not interested in the *ongoing*, resting-state lags between voxels, but in the *evoked* lag responses. The averaging process makes the evoked response more prominent, and the ongoing processes less prominent. We calculated the lags between brain voxels using the time-locked averaged time series. We set the locking time for the component 1 to the last scan labeled as stage 1 or 2, and we estimated for each of the 55 sessions two time lag matrices, one per component (component 1 and 2 time series were of 8 and 11 scans duration, defined according to Fig. 3a). For this analysis images were resliced to a voxel size of $5 \times 5 \times 5$ to make it computationally feasible.

3.2.2. *Findings*

Brain renders show the time delay structure at a voxel level; negative values indicate that the signal structure at that voxel comes before, on average, than the signal in all other voxels in the brain, whereas positive values indicate that the signal at that voxel comes after the signal in all other voxels in the brain. A pattern in line with that of Fig. 3 emerges from

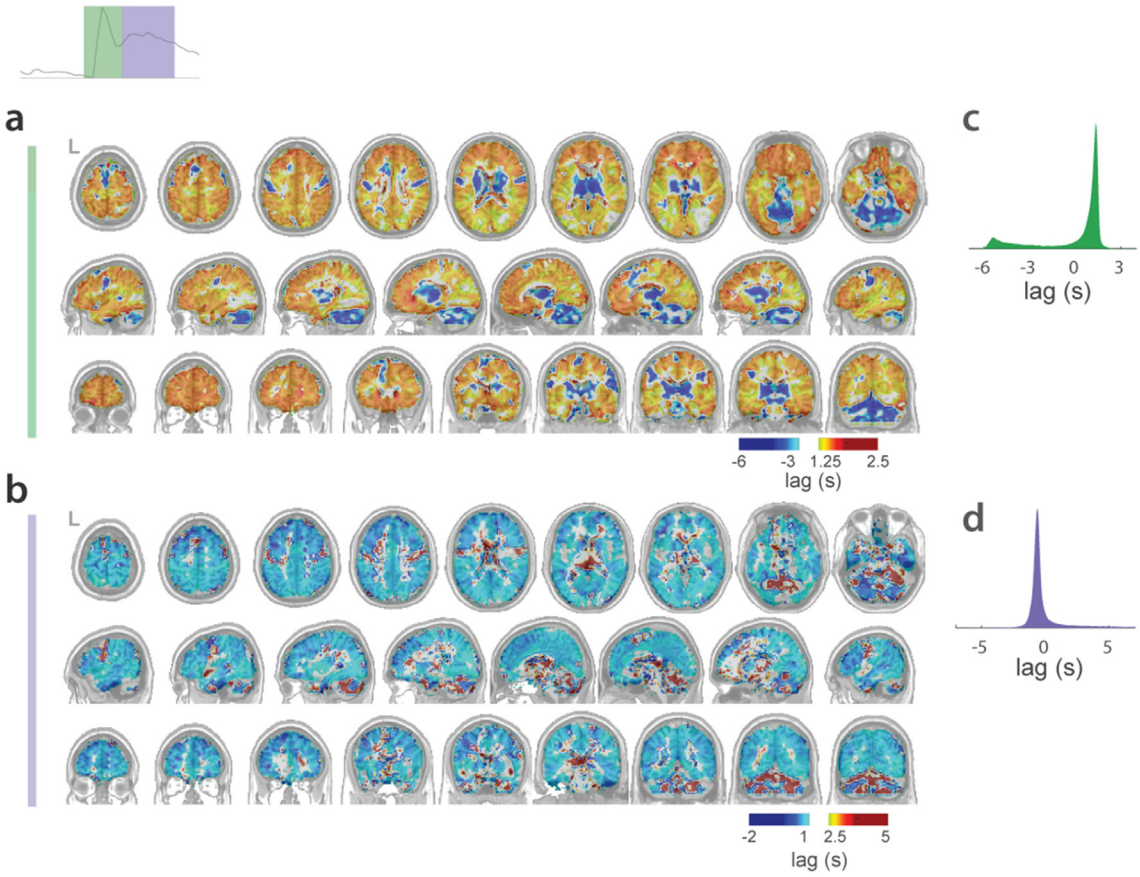

Fig. 4 – Lag structure of the two-component process. We estimated the time-lag structure between voxel pairs across the brain, independently for the previously defined components 1 (a) and 2 (b). Negative values indicate that the signal at that voxel comes before, on average, than all other voxels, whereas positive values indicate that the signal at that voxel comes after. c) and d) histograms of whole brain lags.

this analysis when observing the average across participants (Fig. 4): For the first component, subcortical structures (thalamus, cerebellum and pons, but also right insula and bilateral somatosensory cortices) precede in time most cortical regions (Fig. 4a), especially frontal and parietal ones. The second component seems to display the reversed pattern (Fig. 4b, d): cortical regions (except the sensorimotor ones) the ones that precede subcortical structures, cerebellum and sensorimotor cortices. At the individual level, this pattern is observed for participants 1 and 3 (Fig. 5a), while for participant 2 we obtained the same lag pattern for components 1 and 2 (suggesting that component 1 extends in time, and the pattern found for component 2 in the other participants is absent). We performed a *t*-test for each participant to display the effect size of this analysis. We set the *p*-value to .01 uncorrected for display purposes.

We then calculated the average lag for each functional network for both components (Fig. 6). We obtained the time lags of all ROIs and plotted them in a timeline. Subcortical and sensorimotor networks precede higher order cortices in component 1 (Fig. 6a), a pattern that seems to reverse in component 2 (Fig. 6b) only for participants 1 and 3. Participant 2 displays the same pattern for both components (Fig. 6a–b).

4. Discussion

We explored the process of waking up from early sleep stages due to stimulation and found evidence suggesting that it is a rapid event involving both cortical and subcortical structures. Subcortical and sensorimotor regions seem to be the first regions responding to external stimulation, followed by most of the cortex. After this initial burst of activity, the pattern reverses; cortices activate before subcortical and sensorimotor structures. It should be taken into consideration, however, that due to the highly unique sample we are analyzing, our statistical power is very small, forcing us to perform a qualitative assessment and limiting the generalizability of our results.

Our results are in line with a large body of literature in rodents pointing to the role of subcortical structures in the maintenance of the wake condition through a reciprocal excitation with the cortex. Anterior cingulate cortex (ACC), medial cingulate cortex, thalamus and bilateral insula were among the regions significantly involved in the waking up condition. These regions are part of the salience network, a brain network involved in detecting salient stimuli and self-awareness, and organizing the interplay between different other networks such as Default Mode and Fronto-Parietal

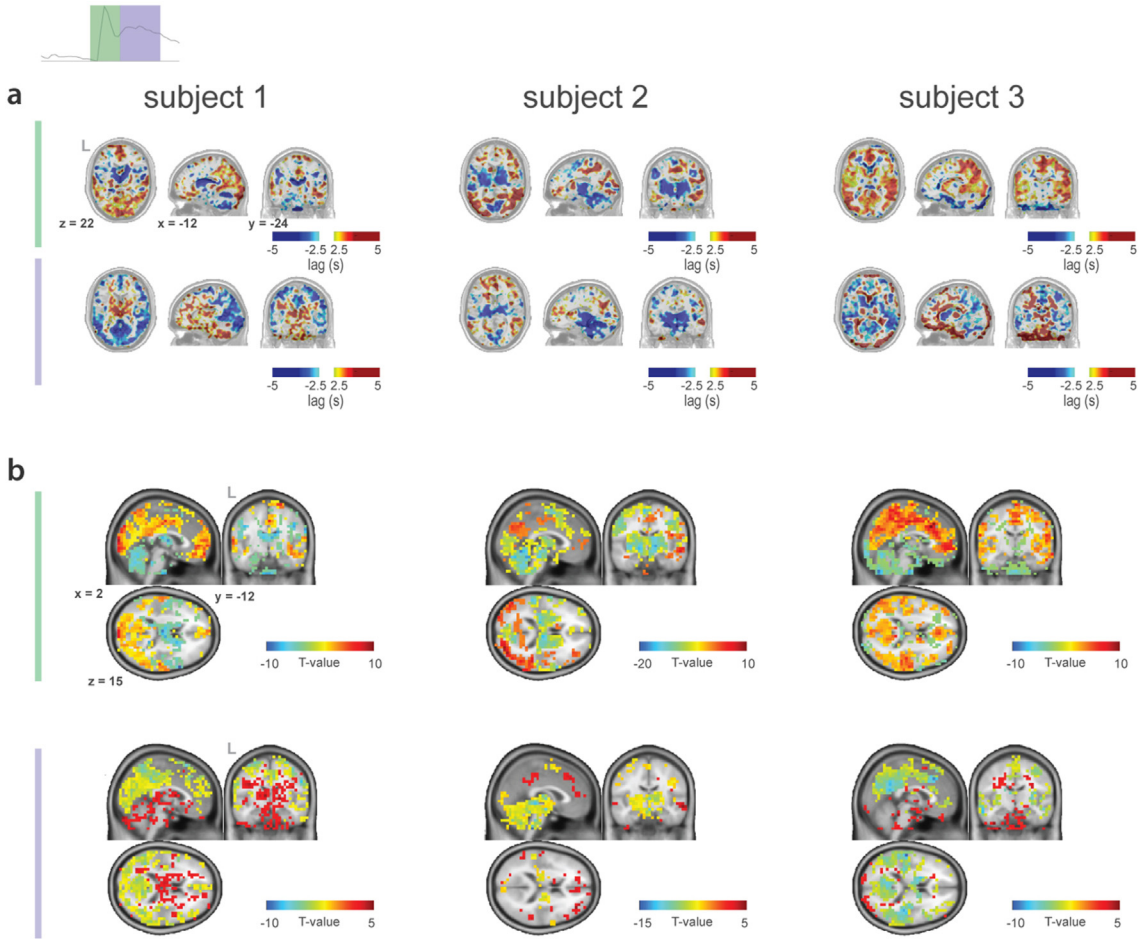

Fig. 5 – Lag structure for single participants. a) While all 3 participants display the same pattern for component 1 (subcortical regions preceding cortical ones), component 2 is only observed in participants 1 and 3 (cortical regions preceding subcortical ones). b) Intra-participant *t*-test of the lag structure. *p*-value was set at .01 for display of the size effect purposes.

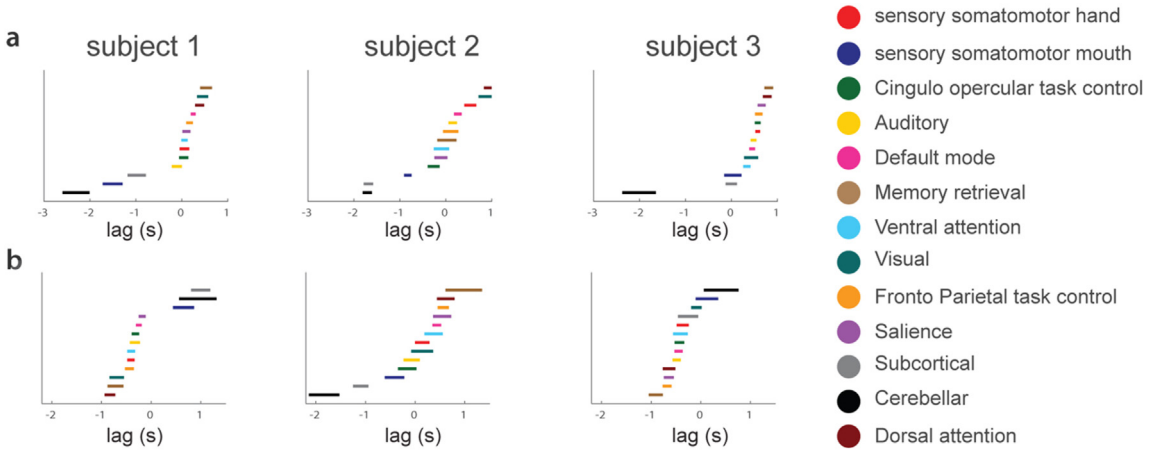

Fig. 6 – Lags and functional networks. a) Average time lag for each functional network for each participant and component. Error bars represent the s.e.m. For all participants, in component 1 subcortical and cerebellar networks are activated first, a pattern that is reversed for participants 1 and 3 in component 2 (b), but not for participant 2 (who replicates the same component 1 pattern).

networks (Menon & Uddin, 2010; Peters, Dunlop, & Downar, 2016), and thus involved in externally-oriented attention and internally-oriented or self-related cognition. The insula, for instance, has a strong reciprocal connectivity with wake and sleep-promoting hypothalamic and brainstem regions, regulating patterns of sleep and wakefulness. In rats with fronto-insular damage, total awake time diminishes, while total sleeping time increases (Chen et al., 2016). Moreover, the functional connectivity of the anterior insula predicts the recovery of patients with disorders of consciousness (Zhang et al., 2018). Furthermore, the electrical disruption of the anterior insula (AI) can impair conscious awareness (Koubeissi, Bartolomei, Beltagy, & Picard, 2014). The overall picture of our data suggests that salience network (through its main hubs in thalamus, insula and ACC) responds to external stimuli and initiates the process of waking up.

5. Hypothesis generation

The cortical-subcortical pattern of activation we observe should be interpreted in light of current theories of consciousness; especially those emphasizing the role of the arousal circuits. Theories of consciousness differ on whether the induction of consciousness is mainly governed by the thalamo-cortical arousal circuits—the thalamic "off-switch" (Barttfeld et al., 2015; Schiff, 2008; Schroter et al., 2012)—or by the ignition of a fronto-parietal cortices connection (Alkire, Hudetz, & Tononi, 2008; Dehaene & Changeux, 2005; Ferrarelli et al., 2010). Our results suggest that, whereas both the thalamic (subcortical) off-switch and a cortical ignition are involved, subcortical structures precede the cortex. Our results can be framed within the Global Neuronal Workspace Theory (GNWT) (Dehaene & Changeux, 2011; van Vugt et al., 2018), which aims at explaining the process of *conscious content*, rather than the recovery of the *state of consciousness*. This theory of perceptual awareness states that a stimulus reaches awareness by propagating from perceptual cortices to higher cortices in the cerebral hierarchy, where it elicits an "ignition"—a nonlinear event that causes information to become sustained and broadcasted back through recurrent interactions among many brain areas (Dehaene & Changeux, 2005; van Vugt et al., 2018). As a result, a stimulus becomes consciously perceived. Our findings suggest that an analog process takes place during the recovery of the state of consciousness: subcortical and sensory structures seem to ignite the activity in the cortex for the recovery of the *state of consciousness*, just like sensory regions cause the ignition of *conscious content*. This similarity is not unexpected, since the recovery of consciousness co-occurs with the ignition of a specific conscious content: the sudden perception of our environment and ourselves. Our results are of course not conclusive, since our experimental design is not optimal for these questions, including 1) the lack of a clean GLM contrast, since the waking up sound is not the same as the control sound (i.e., part of the activation we observe could be an effect of hearing one's name); 2) the lack of statistical power because of the sample size; and 3) the lack of more profound sleep stages in our data. Our analysis should be replicated and extended using an experimental design specifically conceived to test the hypothesis that recovering consciousness follows a dynamics similar to the well-characterized access to consciousness, with a subcortical ignition process that may drive frontal and parietal cortices.

Author contributions

TH organized the data. SA and PB had the idea for the analysis. SA, AR ACM, JS and PB performed the analysis. All authors wrote the paper.

Pre-registration status

No part of the study procedures or analysis was pre-registered prior to the research being conducted.

Open practices

The study in this article earned an Open Data badge for transparent practices. Code and data are available at https://github.com/alcaides/lag-structure-sleep.

Declaration of competing interest

There are no competing interests.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cortex.2021.06.005.

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