Time-of-day influence on resting-state fMRI: an overlooked factor contributing to the replication crisis?

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Abstract

Findings from neuroimaging studies show low replication rates, but the origin of the problem is not clear. The current project explored the extent of the time-of-day dependent metabolic variation to the replication crisis. Using data from the human connectome project (HCP) release S1200, cross-spectral density dynamic causal modelling was used to analyse time-dependent effects on the hemodynamic response and effective connectivity parameters in the spontaneous fluctuations (>0.1Hz) of the blood oxygenation level dependent (BOLD) signal. Hierarchical group-parametric empirical Bayes found no support for time-of-day variations in effective connectivity, whereas the hemodynamic parameters exhibited a significant time-of-day dependent effect. It is concluded that these findings urge the need to account for the time of day in data acquisition of future MRI studies. Moreover, data from the human connectome project suggest that the relationship between functional and dynamic connectivity and the BOLD signal might not be direct.

Replication Crisis, Resting state fMRI, Circadian, Time of day, Effective connectivity, BOLD, DCM analyses

Introduction

During the last two decades there has been an exponential increase in number of publications related to brain functional connectivity (FC), as measured by functional magnetic resonance imaging (fMRI) (Pawela & Biswal, 2011). The field still rapidly growing, to date boomed covering variety of disciplines, such as neurology, psychiatry, and oncology (Fox & Greicius, 2010; Woodward & Cascio, 2015; Bruno, Hosseini, & Kasler, 2012; Raichle, 2015).

Resting-state functional connectivity (rs-FC) measures temporal correlation of a spontaneous BOLD signal among the different brain regions. Current evidence suggests that the changes or disruptions in the rs-FC may serve as a biomarker of brain disease, such as dementia (Broyd et al., 2009) and other neurodegenerative diseases (Brier et al., 2012), in particular deficits in cognitive performance, associated with Alzheimer's disease, mild cognitive impairment, autism spectrum disorders, and schizophrenia are reflected in the rs-FC (Zhou et al., 2013, Hull et al., 2016, Sheffield & Barch, 2016).

Lately the attention has been drawn to low reliability of neuroimaging studies, with only 39% rate of replication (Open Science Collaboration, 2015). Several factors can contribute to a low reproducibility of brain imaging essential for diagnosis and characterization of brain functions. A recent publication on large scale UK Biobank data indicates that individual differences in cognitive performance are reflected in the rs-FC, specifically DMN, but the neural associations are also shared with individual differences in educational attainment and household income (Shen et al., 2018). Another explanation of a low replication rate is the fact that stimulus-related BOLD responses in most brain areas are found to change across the day, with a typically decrease from morning to evening hours (Marek et al., 2010). A diurnal brain dynamic are also evident in literature concerning attention, and urges that psychological, neuropsychological assessments together with work and school schedules, should be rather programmed in accordance with circadian rythmicity, age, and individual chronotype, rather than based on social and economic considerations, as the former is not easily adjusted (Valdez, 2019). Studies applying forced desynchrony protocol confirm that synchronized alternations between bursts of action potentials and periods of membrane hyperpolarization of cortical neurons are directly modulated by endogenous circadian rhythmicity (Lazar, Lazar, & Dijk, 2015). Consequently, chronotype markedly influence time-of-day modulation on cerebral activity patterns, where studies suggest that larks and owls exhibit an inverted relationship curve during the time-of-day

(Christie & McBrearty, 1979; Horne, Brass, & Petitt, 1980). Notably, brain imaging studies using cognitive performance suggest that some but not all tasks vary throughout the day. For instance, insight based problem performance is shown to increase at "non optimal" time-of-day, contrary to the performance of solving analytical problems (Wieth & Zacks, 2011).

In spite of the endogenous nature of circadian rhythms in several brain functions, the time-of-day dependent variability in resting-state fMRI is not consistently reported. Functional connectivity in the DMN is reported to exhibit a rhythmic pattern, with its peak in the morning and low in the later hours of the afternoon (Blautzik et al., 2013). Additionally, the time-of-day effect has been reported in the medial temporal lobes (MTL) when comparing morning and evening scans (Shannon et al., 2013). When the magnitude of cerebral blood flow and functional connectivity in the DMN is examined, a consistent decrease in DMN functional connectivity, particularly in posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) across daytime is found (Hodkinson et al., 2014). Recent reports do support the notion that functional connectivity in the DMN is affected by time-of-day and chronotype (Facer-Childs, Campos, Middleton, Skene, & Bagshaw, 2019) and a steady decrease of global signal fluctuation and regional BOLD fluctuations together with whole-brain rs-FC throughout the day (Orban et al., 2020). Orban and colleagues (2020) further present evidence, that association between time-of-day and the reductions in global rs-FC is stronger, than association with fluid intelligence measure. Given the above, it is possible to suggest that time-of-day has an influence on rs-FC.

Cortical excitability, white matter microstructures, brain volume, grey matter density, cortical surface and thickness are also measures found to be time-of-day dependent (Voldsbekk et al., 2020, Karch et al., 2019, Nakamura, Brown, Narayanan, Collins, & Arnold, 2015; Huber et al., 2013; Trefler et al., 2016). Nakamura and colleagues (2015) report that brain volume changes significantly across the day, with larger brain volumes in the morning compared to the evening. The authors suggest that the volume changes might be associated with the level of individual hydration. Indeed, hydration level has an effect on the evoked BOLD signal (Kempton et al 2011), however volume changes are observed across multiple populations, i.e. healthy elderly, but also patients suffering from multiple sclerosis, mild cognitive impairments, and Alzheimer's disease when compared with healthy subjects Nakamura et al., 2015). Morphometry measures suggest that increased volumes of cerebrospinal fluid CSF are associated with decreased volumes of grey and white matter (Trefler et al., 2016) and that the extracellular space volume is reduced in large parts of the white matter from morning to evening (Voldsbekk et al., 2020).

A number of factors may introduce bias, especially in clinical neuroimaging literature and longitudinal studies, and might be misinterpreted as possible individual difference, whereas the difference is rather rooted in the timing of the acquired scan (Trefler et al., 2016; Voldsbekk et al., 2020; Karsch et al.,2019). Further investigation of time-of-day effects on neuroimaging is much needed. Further, low replicability rates to date in rs-FC literature indicate an immediate need of consensus within the findings. The aim of the current study was to investigate diurnal change of effective rs-FC and neural metabolic response measured by BOLD signal. For the scope of this study, three large scale rs-FC networks were selected, the DMN, Saliency Network (SN) and Central Executive Network (CEN), and compared at six different time-spans across the day (from 09:00 until 21:00). It was expected to observe diurnal change in neuronal activity and/or metabolic response (BOLD signal).

Method

The Human Connectome Project initiative data release "S1200" was used in the current study, for more information about the data please see Van Essen et al., 2013 (http://www.humanconnectome.org).

Participants

For the purposes of the current study the participants scanned from 9:00 h to 21:00 h were selected from the complete dataset "S1200". The mid-scan time was used to allocate the participants into 6 groups of selected time-spans (9:00 h - 10:59 h, N=96; 11:00 h - 12:59 h, N=100; 13:00 h - 14:59 h, N=100; 15:00 h - 16:59 h, N=100; 17:00 h - 21:00 h, N=98), in total 594 participants (310 females).

All participants were healthy adults ranging from 22 to 35 years of age. The age distribution of the sample used in this study 22-25 years, N=122; 26-30, N=257; 31-35, N=207; 36+, N=8. The data was collected over 3 years on a single 3 Tesla (3T) scanner. The participant pool primarily consisted of subjects living in Missouri, in families with twins. Exclusions criteria were neurodegenerative disorders, documented neuropsychiatric disorders, neurologic disorders, high blood pressure and diabetes. For a complete list of inclusion criteria please see Van Essen et al., 2013 (Table S1)).

Procedure

Participants were scanned at the Washington University, US over a two-day and one-night visit. An informed consent was signed by the participants at the beginning of day 1. In

accordance with previously run pilot studies a consistent scanning schedule was maintained for all the participants in the study, unless a re-scan was required, for more details see Van Essen and colleagues (2013). A mock scanning trial with feedback on head motion was run prior to the first scanning. The scanning occasions were scheduled once a day, one on day 1 and the other on day 2. The averaged time for each scanning occasion was 15 minutes during which the room was darkened. The participants were asked to lay still with their eyes open and fixate their gaze at a bright fixation cross in the dark background. The clock time for each scanning day varied from 7:00 h to 22:00 h. Complete data collection procedure can be found in Van Essen et al., 2013.

Image Acquisition

Resting-state fMRI data collection was carried out in accordance with an optimized fMRI image acquisition protocol as determined by the Human Connectome Project piloting. A custom Siemens 3T "Connectome Skyra" scanner was used to record the data for all participants. The scanner was equipped with a 32-channel head coil, custom gradient coils and gradient power amplifiers boosting the gradient strength to 100 mT/m. Resting-state fMRI data was acquired in two sessions: first 2x15 minute runs, Right/Left and Left/Right phase encoding day one, and second 2x15 minute runs Left/Right and Right/Left phase encoding day two, a total of 1 hour resting-state fMRI. A gradient-echo multiband EPI imaging sequence was used to acquire resting-state fMRI data. Resting-state fMRI image acquisition settings were as follows: repetition time (TR) of 720 ms, echo time (TE) of 33.1 ms, 52° flip angle, field of view 208x180 mm (readout x phase encoding), slice thickness 2.0mm; 72 slices; 2.0 mm isotropic voxels and a multiband factor of 8 (for more information see Glasser et al., 2016; Uğurbil et al., 2013). In addition, high resolution T1-weighted structural images were obtained with the following parameters: TR 2400 ms, TE 2.14 ms, inversion time (TI) 1000 ms, flip angle 8°, FOV 224x224mm and 0.7 mm isotropic voxels (Uğurbil et al., 2013).

Image processing

For the purpose of this study the data was acquired pre-processed in accordance with "Human Connectome Project minimal pre-processing pipeline" please see Glasser et al., 2013 for details. Standard pre-processing steps such as: correcting for distortions and spatial alignment were performed. In addition to the mentioned standard procedures the data was also corrected for spatial distortions, aligned across modalities and brought into a standard spatial

atlas coordinate system. The only variation from standard pre-processing procedures was due to the bore diameter of the scanner being 56 cm, which is smaller than the standard Siemens 3T Skyra size (70cm diameter), the reduced diameter and lack of a customized patient table resulted in a higher placement of patient table in the bore and the participants head not being centered along the gradient isocentre, meaning the scans have greater than normal gradient distortions, which have been corrected for in the Human Connectome Project pre-processed data used in this project, for more details see Van Essen et al., 2013.

Analysis

There were 8 regions of interest selected for the current study: four nodes in the DMN (mPFC; PCC; right inferior parietal cortex, RIPC; left inferior parietal cortex, LIPC), two nodes of saliency network (SN) (anterior insula, AI; anterior cingulate cortex, ACC) and two nodes of central executive network (CEN) (dorsolateral prefrontal cortex, DLPFC; posterior prefrontal cortex, PPC). For exact coordinates of each ROI please see appendix 1. Each ROI was a sphere of 6 mm diameter. Cross-spectral-density dynamic causal modelling (csdDCM) implemented in SPM 12.2 was used to extract time series for each ROI (Friston et al., 2014).

The effective connectivity was estimated for each participant. The PEB (Parametric Empirical Bayes) framework was used to estimate the joint effective connectivity per time-span (Zeidman et al., 2019).

A hierarchical PEB was applied to test varying design-matrices against the time-of-day model. First, a PEB analysis was conducted for each time-span separately using Bayesian model comparison. Thereafter, the corresponding PEB results were subjected to a series of second level PEB analyses, where four models for time-of-day effects were explored. 1) Model 1-6: expectation of a *deviation from the mean for one single time-span*, 2) Model 7-11: expectation of a *deviation from the mean over two time-spans*, 3) Model 12-17: expectation of *phase-shifted variants of a sinusoid function* - representing a circadian rhythm, peaking at different time spans, 4) The null-model*:* expectation of *no predictions at any time-span*. The winning model was explored at a cut-off of posterior probability of $Pp > 0.95$. These analyses were conducted for the effective connectivity matrix (A-matrix, 8 x 8 parameter).

Then, the Bayesian model were compared to hemodynamic parameters of the Balloon model; *transit time*, *epsilon* and *decay* and the parameters α (reflecting amplitude) and β (reflecting the spectral density of the neural fluctuations). The parameter *transit time* was estimated for each of the eight ROIs, and *decay*, *epsilon,* α, and β are global parameter.

Results

Second level PEB analyses of the time-of-day variations in the effective rs-FC showed that the highest model evidence (model accuracy minus model complexity) was the Null model (see ***Figure 1a***). The effective connectivity matrix of the Null model with a posterior probability > 0.95 (pp; the updated probability of the model being true after comparison with other models) is displayed in ***Figure 1b***. In other words, the Bayesian model suggests that the neural activity in large scale networks remain stable throughout the day.

Comparing effective connectivity (Bayesian model) with hemodynamic parameters (Balloon model), both amplitude (α) and spectral density (β) favoured model 7, prediction of a deviation from the two time-spans early in the morning, 09-13 h (see ***Figure 1c***). Moreover, three models all variants of the winning model by predicting a deviation before noon received a high log-evidence (***Figure 1c***); between 11-13 h (model 2); as a sinusoid function peaking between 11-13 h (model 12) or being the inverted wave form with a minimum between 11-13 h (model 15). Group means relative to the fitted model are shown in ***Figure 1d***. The posterior values seen in ***Figure 1e*** represents the level of parameter movement in accordance with the winning model (model 7) at the pp>0.95 level. The posterior values for the *decay* and the *amplitude* of the CSD function are significantly reduced for the time span 9-13 h (model 7). Finally, ***Figure 1f*** displays how the posterior values for decay and amplitude vary over the day, after the respective DCMs were averaged for each time-span, using Bayesian Model Averaging. In other words, the neural metabolic response measured by BOLD.

FIGURE 1 ABOUT HERE

Discussion

To the best of our knowledge this study is the first to investigate the time-of-day influence on resting-state neuronal activity (dynamic connectivity) and metabolic demand (BOLD signal). The results from the current study suggest that while the neuronal activity of the brain remains stable throughout the course of day, the metabolic demand exhibits a variation between the selected time-spans.

The effective connectivity in three large-scale resting-state networks, namely DMN, CN, and CEN, was found to remain fairly stable across morning, noon and evening hours (from 09:00 to 21:00). A stable DMN throughout daytime is in contrast to differences in functional connectivity found in the DMN and MTL when comparing morning and evening scans (Blautzik et al., 2013, Shannon et al., 2013). Furthermore, the present findings are not in

line with the most recent publication, using the subjects from the Human Connectome Project release S1200, reporting GS cumulative decrease and whole brain FC decrease associated with the time of day (Orban et al., 2020).

This inconsistency between the findings of the current study and previously reported results is likely rooted from the different methodological approaches used. In the present study the dynamic relationship between functionally connected nodes were assessed using a generative model, namely Dynamic Causal Modelling (DCM), which analyses the bidirectional effect each network exhibits with itself and others. By contrast, previous publications reported the functional connectivity, namely the correlational relationship between the nodes of the network, which is based on the temporal correlations of the BOLD signals (Facer-Childs et al., 2019; Orban et al., 2020). The main finding of our results is that the latter indeed shows a time-of-day effect, and, hence, methods that are based on directly analysing the amplitude of the BOLD signal may be affected by the time-of-day effects. These effects might be caused by, for example, diurnal variations in the blood pressure (Millar-Craig, Bishop & Raftery, 1978).

The BOLD signal, according to the current findings, varies depending on the time-of-day, in particular between morning and afternoon, regardless of the dynamic network activity. The hemodynamic parameter *decay* and the *amplitude* of the CSD function all exhibited a significant relationship with the time-of-day dependent model (model no. 7) (***Figure 1e***). The *decay* parameter reflects the rate of signal elimination (Friston et al., 2000). A decrease in this parameter indicates an increased resting cerebral blood flow (rCBF) and a faster elimination of the signal and may also cause a larger BOLD undershoot. Accordingly, the BMC-selected model predicts a faster decaying BOLD signal before noon and, subsequently, a slower BOLD signal decay in the afternoon. As the plot over time indicates (***Figure 1f***), this appears to be a dynamic effect over the daytime, and the inclusion of further time-spans may show a cyclic effect. A similar effect can be seen when examining the *amplitude* of the cross-spectral-density function that also demonstrates a lower amplitude in the morning than afternoon. In contrast to the *decay*, CSD *amplitude* showed a pronounced minimum for the 11-13 time-span. This different temporal evolvement during the morning does also explain why all four models that showed high model evidences in BMC (***Figure 1c***) were rated similarly. Interestingly, there were no region-specific effects in the *transit times*, which indicates that this is a global vascular effect.

The shift of *decay* is in line with the studies on resting state, where the connectivity appears higher in the morning compared to the evening (Hodkinson et al., 2014). The time-of-

day dependency of the BOLD signal as observed in varied *decay* and *CSD amplitude* parameters, is supported by previously published results on brain volume (Karsch et al., 2019, Nakamura et al., 2015; Trefler et al., 2016). The increase in *decay,* as seen in the current study occurs in the morning as well as the previously reported reduction of CSF in Trefler and colleagues (2016), where an inverse relationship between the two is observed in the afternoon. Given that CSF is vital for regulating the CBF, it is plausible to speculate, that the reduction in the rCBF caused by a peak in the time-spans before noon (9-11 until 11-13) is associated with the lower levels of CSF. During the first half of the daytime a decrease in blood pressure, heart rate, and CBF(V) is observed around 11-13, whereas, cortisol is still high. These daily changes in blood parameters provides support for the described change in the hemodynamic parameter. It is reasonable to observe a slower BOLD response with the reduced CBF, and it is likely that the *decay* is dependent on vascular signalling and relaxation time (Friston et al., 2000).

The authors of former publications controlled for chronotype, sleep duration, and quality (Blautzik et al., 2013; Shannon et al., 2013). In contrast, the current work was carried out on open access data that did not include information on chronotype or any sleep dept. A recently published work by Facer-Childs and colleagues (2019) suggests that there are significant differences in functional connectivity between early and late chronotypes in the DMN (Facer-Childs et al., 2019). These differences are somewhat in line with early findings of Merrow et al. (2005), and Weitzman et al. (1971), suggesting that different chronotypes have distinct rhythmicity patterns throughout the day, where the post lunch dip and morning rise in cortisol levels might differ (Merrow et al., 2005; Weitzman et al., 1971). Taking into account these reported significant differences, it might be plausible, that the reported effects from the current study could have been even stronger, if accounting for different phenotypical profiles would have been possible.

The main impact of the presented results, however, is to be seen in the context of past and current discussions on the reliability of fMRI studies (Specht, 2019; Specht, Willmes, Shah, & Jäncke, 2003). The fact that the significant time-of-day effect only occurred in the hemodynamic but not in the connectivity parameter has a critical implication for past, current, and future research studies. The results from research on group differences, which did not counterbalance or did not account for the time of scanning might have been in turn detecting the time-of-day differences rather than the true group differences, for instance when a group of participants is examined during morning hours (e.g. patients) and another group in the evening (e.g. control group). This may turn out to be one of the factors contributing to the low

rates of replicability (Open Science Collaboration, 2015). Further, the use of dynamic causal modelling in future studies could explain the true nature of the relationship between BOLD signal and neural activity. These future achievements would heavily contribute not only by bringing consensus in diurnal rhythmicity and resting-state connectivity research but also for in-depth understanding of brain activity.

There are some limitations to the current work, that could be addressed in future studies. First and foremost, the data obtained from the Human Connectome Project, even in high quality, was not collected in order to address the connectivity differences across the time-of-day and did not account for chronotype differences. Secondly, the analysis method used in the present study (DCM) differentiates between the hemodynamic response and brain activity measures, but no additional parameters that have been shown to affect resting state connectivity could be included, such as blood pressure, cerebral blood flow (Facer-Childs et al., 2019; Specht, 2019). Finally, the study relied on between subject design, i.e. different subjects were randomly assigned to the time-spans, whereas in order to obtain a truly comprehensive understanding of the circadian rhythmicity, a repeated measure (within subject design) would be best, where the same participant would undergo scanning at each time-span (Karch et al., 2019).

In summary, the results from the current study contribute to the limited body of literature on time-of-day changes in the brain. The findings suggest, that even though there is an observed variability during the course of the day in the hemodynamic response, which is captured by fMRI, the neuronal activity remains stable. The changes in the hemodynamic response possibly reflect the influence of time-of-day effects of the metabolic and vascular system. This may indicate that the BOLD signal is more susceptible to exogenous parameters than the brain activity itself. These findings urge the need of further separation between the hemodynamic response and neural activity since the relationship between the two might not be direct and more importantly not stable throughout the day.

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Figure 1

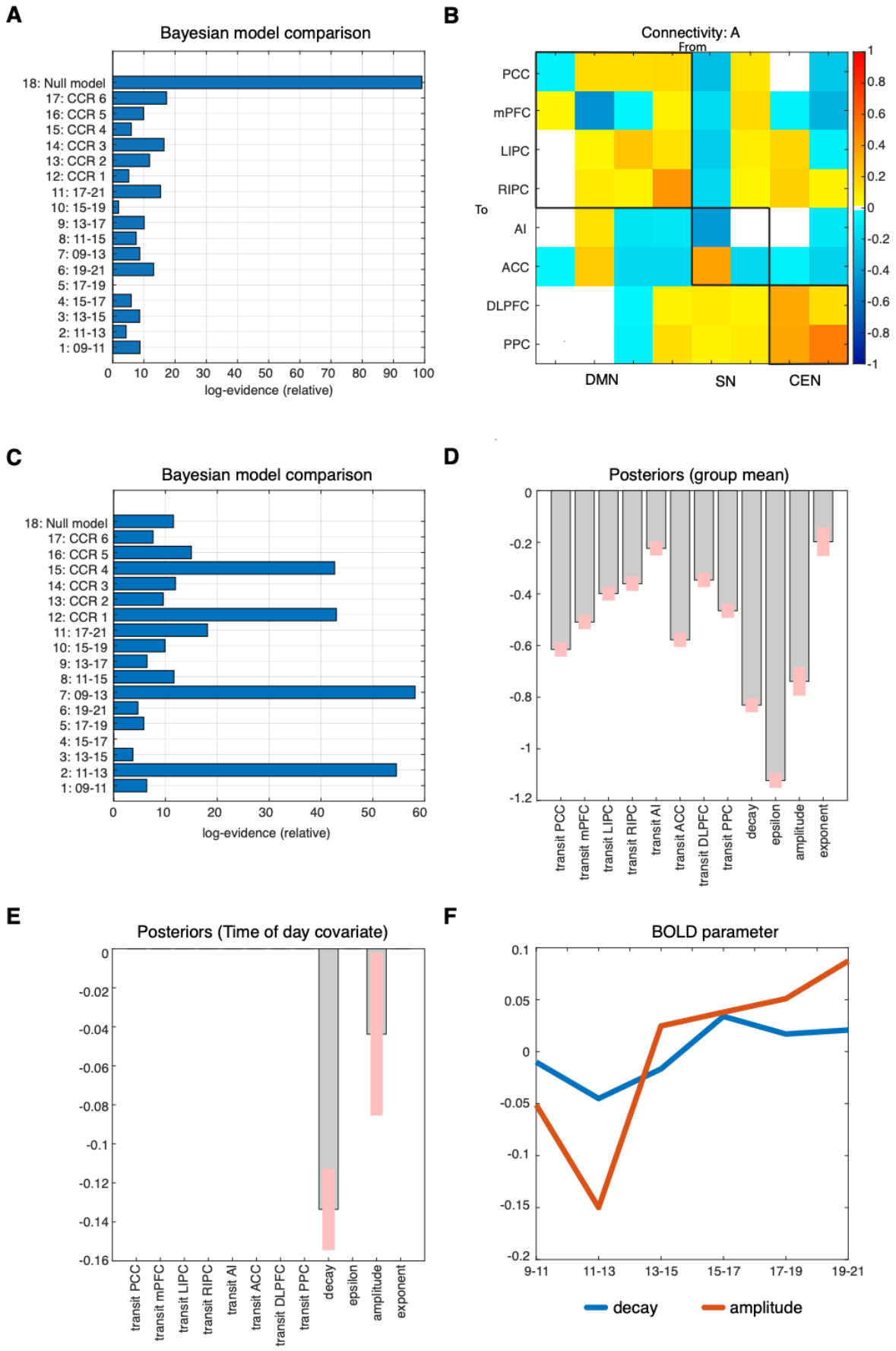
A
Bayesian model comparison
18: Null model
17: CCR 6
16: CCR 5
15: CCR 4
14: CCR 3
13: CCR 2
12: CCR 1
11: 17-21
10: 15-19
9: 13-17
8: 11-15
7: 09-13
6: 19-21
5: 17-19
4: 15-17
3: 13-15
2: 11-13
1: 09-11
0 10 20 30 40 50 60 70 80 90 100
log-evidence (relative)
B
Connectivity: A
From
To
PCC
mPFC
LIPC
RIPC
AI
ACC
DLPFC
PPC
DMN
SN
CEN
1 0.8 0.6 0.4 0.2 0 -0.2 -0.4 -0.6 -0.8 -1
C
Bayesian model comparison
18: Null model
17: CCR 6
16: CCR 5
15: CCR 4
14: CCR 3
13: CCR 2
12: CCR 1
11: 17-21
10: 15-19
9: 13-17
8: 11-15
7: 09-13
6: 19-21
5: 17-19
4: 15-17
3: 13-15
2: 11-13
1: 09-11
0 10 20 30 40 50 60
log-evidence (relative)
D
Posteriors (group mean)
0 -0.2 -0.4 -0.6 -0.8 -1 -1.2
transit PCC
transit mPFC
transit LIPC
transit RIPC
transit AI
transit ACC
transit DLPFC
transit PPC
decay
epsilon
amplitude
exponent
E
Posteriors (Time of day covariate)
0 -0.02 -0.04 -0.06 -0.08 -0.1 -0.12 -0.14 -0.16
transit PCC
transit mPFC
transit LIPC
transit RIPC
transit AI
transit ACC
transit DLPFC
transit PPC
decay
epsilon
amplitude
exponent
F
BOLD parameter
0.1 0.05 0 -0.05 -0.1 -0.15 -0.2
9-11 11-13 13-15 15-17 17-19 19-21
decay
amplitude

Figure Legend

Figure 1: *The figure summarizes all results from the hierarchical Parametric Empirical Bayes analysis*

a. Bayesian Model Comparison on the connectivity parameter, where model 1-6 assumes deviating effect only for single time-spans of two hours, while model 7-11 assumed deviating effects for time-spans of four hours. The model 12-17 modelled different phase shifted version of an idealized circadian rhythm. Model 18 was the null model that assumed no time-of-day effects

b. The estimation of effective connectivity (from columns to rows) across all subjects. The leading diagonal elements represent self-connections in logarithmic-scale relative to the prior mean of -0.5 Hz. White space represents no significant effect at pp level > 0.95

c, Bayesian Model Comparison on the hemodynamic parameter *transit time*, *decay*, *epsilon*, as well as *Cross-spectral-density amplitude* and *Cross-spectral-density exponent*

d. Group means for the posterior estimates of the hemodynamic parameter, displayed at a posterior probability of pp>0.95

e. Posteriors of the winning model, displayed at pp>0.95

f. Time course of the two significant posteriors decay and CSD amplitude after time-span-wise averaging with Bayesian Model Averaging