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ORIGINAL ARTICLE

# Testing Proposed Neuronal Models of Effective Connectivity Within the Cortico-basal Ganglia-thalamo-cortical Loop During Loss of Consciousness

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## Abstract

In recent years, a number of brain regions and connectivity patterns have been proposed to be crucial for loss and recovery of consciousness but have not been compared in detail. In a 3 T resting-state functional magnetic resonance imaging paradigm, we test the plausibility of these different neuronal models derived from theoretical and empirical knowledge. Specifically, we assess the fit of each model to the dynamic change in effective connectivity between specific cortical and subcortical regions at different consecutive levels of propofol-induced sedation by employing spectral dynamic causal modeling. Surprisingly, our findings indicate that proposed models of impaired consciousness do not fit the observed patterns of effective connectivity. Rather, the data show that loss of consciousness, at least in the context of propofol-induced sedation, is marked by a breakdown of corticopetal projections from the globus pallidus. Effective connectivity between the globus pallidus and the ventral posterior cingulate cortex, present during wakefulness, fades in the transition from lightly sedated to full loss of consciousness and returns gradually as consciousness recovers, thereby, demonstrating the dynamic shift in brain architecture of the posterior cingulate "hub" during changing states of consciousness. These findings highlight the functional role of a previously underappreciated direct pallido-cortical connectivity in supporting consciousness.

**Key words:** anesthesia, cortico-basal ganglia-thalamo-cortical loop, disorders of consciousness, effective connectivity, posterior cingulate cortex

## Introduction

Understanding the neuronal mechanisms that generate consciousness remains a crucial aim in neuroscience. Currently, a major focus of research is aimed at identifying altered network patterns associated with loss of consciousness during anesthesia, nonrapid eye movement (NREM) sleep, or after severe brain injury (Boly et al. 2013; MacDonald et al. 2015). Besides theories that focus on measures such as integration (Tononi 2010) or broadcast (Baars 2005) at a whole-brain level as a determinant of consciousness itself, a growing amount of research has begun identifying the prominent status of certain cortical and subcortical regions, and their complex interaction involved in various aspects of consciousness. Contents of conscious experience has been related, for example, to lateral aspects of the frontal cortex (Dehaene and Changeux 2011), while the state of consciousness seems to modulate connectivity particularly in medial frontal and parietal cortices (Laureys et al. 1999; Horovitz et al. 2008, 2009; Fernández-Espejo et al. 2010; Vanhaudenhuyse

et al. 2010; Crone et al. 2011, 2014, 2015; Sämann et al. 2011; Boly, Moran, et al. 2012; Monti et al. 2013; Amico et al. 2014). Another frequent finding during altered states of consciousness is that subcortical areas (mainly the thalamus) play a significant role (Adams et al. 2000; Alkire et al. 2000; Laureys et al. 2000; Schiff 2008; Hannawi et al. 2015; Song and Yu 2015). In contrast to the severely criticized study using deep-brain electrode recordings during anesthesia (Velly et al. 2007; Jäntti et al. 2008), recent evidence in rodents suggests that the breakdown of cortical connectivity during unconsciousness is initiated by subcortical neuronal mechanisms in NREM sleep as well as in different types of anesthesia (Baker et al. 2014). This finding is of particular interest since it indicates, on the one hand, that there may be common mechanisms underlying loss of consciousness irrespective of its trigger. On the other hand, it shows that these mechanisms are originated in subcortical regions. However, investigations were performed in rodents and limited to very specific areas within the thalamus and frontal cortex, thus, disregarding possible dynamic influences from other subcortical regions involved in loss of consciousness such as the striatum (Mhuircheartaigh et al. 2010).

Numerous studies investigating arousal and consciousness have stressed the importance of network connectivity within a circuit comprising areas across the striatum, globus pallidus, and thalamus and its reciprocal projection to medial cortices (Dehaene and Changeux 2005; Qiu et al. 2010; Vetrivelan et al. 2010; Lazarus et al. 2012; Lutkenhoff et al. 2015). The literature describes 2 main routes within this circuit, the cortico-basal ganglia-cortical loop and the cortico-basal ganglia-thalamo-cortical loop (Finch et al. 1984; Alexander et al. 1986; Nambu 2008; Saunders et al. 2015). Dysfunctional connectivity of critical areas within this circuit has been highlighted by research in impaired consciousness such as the posterior cingulate cortex (Fiset et al. 1999; Laureys et al. 1999; Horovitz et al. 2008, 2009; Fernández-Espejo et al. 2010; Vanhaudenhuyse et al. 2010; Crone et al. 2011, 2015; Sämann et al. 2011; Boly, Moran, et al. 2012; Monti et al. 2013) and the thalamus (Alkire et al. 2000; Laureys et al. 2000; Lull et al. 2010; Xie et al. 2011; Zhou et al. 2011; Laureys and Schiff 2012; Guldenmund et al. 2013; Baker et al. 2014). In addition, one main hypothesis proposes that impaired consciousness and goal-directed behavior, at least in the context of severe brain injury, is due to the dysfunction of striatal medium spiny neurons and the consequential disinhibition of pallido-thalamic γ-aminobutyric acid-ergic (GABAergic) fibers, thereby decreasing thalamo-cortical neuronal activity (Schiff 2010). In contrast, there is growing evidence suggesting that thalamo-cortical connectivity may be less involved in loss of consciousness in the animal model as well as in humans (Mhuircheartaigh et al. 2010; Silva et al. 2010; Boly, Perlbarg, et al. 2012; Monti et al. 2013).

Collectively, while a number of models regarding the cortico-basal ganglia-thalamo-cortical loop have been presented to explain arousal, consciousness, and behavioral responsiveness across different modalities, these models have been rarely directly compared with one another with respect to their ability to account for empirical data.

The present study was therefore conceived as a means of directly evaluating the effectiveness of proposed models of causal dynamics within the cortico-basal ganglia-thalamo-cortical complex in explaining brain data during propofol-induced loss and recovery of consciousness. By summarizing the recent biological and theoretical evidence, we defined 7 different models (see Fig. 1) representing the different circuits involved and their possible impairments related to loss of consciousness. We applied spectral dynamic causal modeling (spDCM) for resting-state functional magnetic resonance imaging (fMRI) (Friston et al. 2014; Razi et al. 2015) to model the induced neuronal responses, and Bayesian model selection (Stephan et al. 2009) to compare the different models. Specifically, we evaluated (1) which of 7 potential neuronal models best explains the variance of the blood oxygenation level dependent (BOLD) signal across propofol-induced transitions from wakefulness, sedation, loss of consciousness, to recovery, and, (2) which regions are modulated by the level of consciousness in terms of their connectivity strength, amplitude of oscillations, and frequency range.

## Materials and Methods

This study was approved by the Ethics Committee of the Medical School of the University of Liège (University Hospital, Liège, Belgium) and performed according to the principles expressed in the Declaration of Helsinki.

### Participants

In this study, 20 healthy right-handed participants (16 female; age = 18–31 years (M = 22.4; SD = 3.4)) with no history of neurological or psychiatric disease were included. Part of this sample has been investigated, with different methods, in previous studies (Boveroux et al. 2010; Monti et al. 2013). Two subjects were excluded due to incomplete volume acquisition. Written informed consent was obtained from all subjects according to the Declaration of Helsinki.

### Conditions

Participants were scanned 4 times in a row with varying consecutive levels of consciousness as clinically evaluated by the Ramsay scale (Ramsay et al. 1974). The first scan was accomplished with the participants being fully awake (wakefulness). Right after the first scan, the participants were sedated. The second scan was performed when they were still present but their response to verbal commands were slowed (sedation; Ramsay level 3). As soon as the participants experienced loss of consciousness in which they exhibited no response to verbal instruction (loss; Ramsay levels 5–6), the third scan was performed. Finally, the last scan was performed after participants had recovered consciousness (recovery; Ramsay level 2).

### Data Acquisition

Resting-state fMRI data were acquired using a 3 T Siemens Allegra scanner (Siemens AG, Munich, Germany) with an Echo Planar Imaging sequence in 32 ascending slices (time repetition [TR] = 2,460 ms; time echo [TE] = 40 ms; field of view [FOV] = 220 $mm^2$; voxel size = 3.45 × 3.45 × 3 mm; matrix size 64 × 64 × 32). Because the number of volumes obtained across subjects and conditions differed (varying between 196 and 350), correlation matrices were computed only on 195 volumes (8 min) for all conditions and subjects. In addition, $T_1$-weighted MP-RAGE images were also acquired (TR = 2.25 ms; TE = 2.99 ms; FOV = 256 × 240 × 160 mm; FA = 9°; voxel size = 1 × 1 × 1 mm).

### Preprocessing

Neuroimaging data were preprocessed using FSL (Jenkinson et al. 2002). The anatomical images were brain extracted using optiBET (Lutkenhoff et al. 2014). The initial 4 TRs of each functional dataset were considered as dummy scans and were removed. In a next step, data underwent slice-time correction, rigid-body adjustment for intra-run motion, and 4 mm FWHM smoothing.

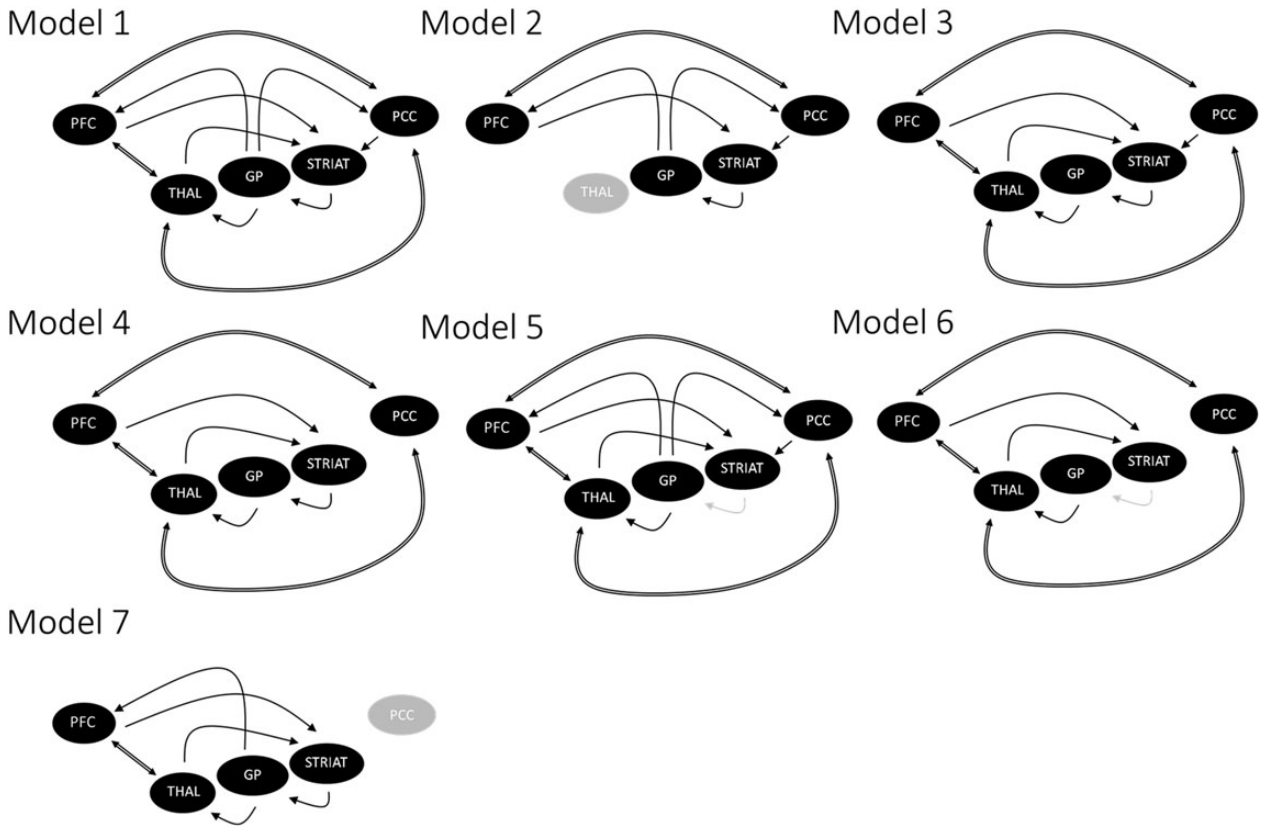


**Figure 1.** Schematic representation of the tested model space. Models were specified on the basis of biological knowledge of the cortico-basal ganglia-thalamo-cortical loop and evidence from the field of research in impaired consciousness, targeting central regions or connections such as thalamus, posterior cingulate cortex, and striatum. Subcortical regions of interest were segmented anatomically on a single-subject basis. Cortical regions of interest within frontal and posterior cortices were selected using single-subject independent component analysis to ensure functional connectedness with the subcortical regions (see Crone et al. (2015) for a similar approach). The tested model space is defined as follows: model #1: the full cortico-basal ganglia-thalamo-cortical loop including direct connections from the globus pallidus to the cortex (Finch et al. 1984; Alexander et al. 1986; Nambu 2008; Saunders et al. 2015); model #2: cortico-basal ganglia-cortical loop (Gritti et al. 1997; Vetrivelan et al. 2010; Saunders et al. 2015) and impaired thalamus; model #3: the classic cortico-basal ganglia-thalamo-cortical loop including the direct and indirect circuit (Saunders et al. 2015); model #4: Schiff's mesocircuit model (Schiff 2010); model #5: full cortico-basal ganglia-thalamo-cortical loop with impaired striato-pallidal connectivity; model #6: Schiff's mesocircuit model with impaired striato-pallidal connectivity (Schiff 2010); model #7: impaired posterior cingulate cortex; PFC, prefrontal cortex; PCC, posterior cingulate cortex; GP, globus pallidus; impaired regions or connectivity are shown in light gray.

The functional images were not transformed into standard space to ensure a more accurate anatomical assignment. Thus, the mean echo planar imaging was registered to the participant's own anatomical scan using advanced normalization tools (ANTs; http://stnava.github.io/ANTs/) and further processing was performed in individual subject space. Voxel size was re-sampled to $3 \times 3 \times 3.75$ mm.

Although differences in DCM based estimates of anatomically defined effective connectivity across conditions as compared with estimates of whole-brain functional connectivity are less likely to be driven by session effects such as motion artifacts differing between conditions (Rowe et al. 2010), additional steps were undertaken to avoid motion confounds. First, framewise displacement calculated from derivatives of the 6 rigid-body realignment parameters were compared across conditions using repeated-measures analysis of variance (ANOVA) to ensure that there are no significant differences in motion ($F = 0.67$, $P = 0.426$). Second, we included specific motion parameters in the general linear model (see Dynamic Causal Modeling).

## Definition of Models

To investigate dynamic interactions, we used a similar approach as in our previous work (Crone et al. 2015). However, there is an important distinction: In the present work, the choice of models was hypothesis-driven instead of exploratory.

The goal of this study is to test whether any specific model better accounts for propofol-induced transitions from consciousness to unconsciousness. Thus, the present investigation of effective connectivity during loss of consciousness is hypothesis-driven. The choice of models tested is based on the knowledge of empirically verified connectivity patterns between the regions associated with arousal and conscious processing. Regions that have been strongly associated with arousal (Qiu et al. 2010; Vetrivelan et al. 2010) and (impaired) conscious processing (Dehaene and Changeux 2005; Schiff 2010; Vanhaudenhuyse et al. 2010; Crone et al. 2011, 2014, 2015; Amico et al. 2014) include the medial frontal cortex, the medial parietal cortex, the basal ganglia, and the thalamus. These regions are known to be anatomically and functionally highly connected forming 2 circuits and their subcircuits involved in motor control, attention, limbic functions, cognitive behavior, and reward learning, the so called cortico-basal ganglia-cortical loop and the cortico-basal ganglia-thalamo-cortical loop (Alexander et al. 1986; Gritti et al. 1997; Nambu 2008; Vetrivelan et al. 2010; Saunders et al. 2015). In order to test the role of these regions and networks in the loss and return of consciousness in humans, we created 7 plausible models by combining 4 different plausible versions of the circuits and 4 different plausible targets

of impairment (see Fig. 1). We note that we compared only 7 models because the mathematical representation of the cortico-basal ganglia-cortical loop and a disconnected thalamus are both expressed in model #2.

The first model we included was a "full" model combining all the evidence from anatomical and functional studies in animals (and few in humans). Findings across studies suggest a closed loop from the cortex sending projections to the striatum which in turn projects to the globus pallidus and from there via thalamus to cortex as well as to cortex directly (Alexander et al. 1986; Albin et al. 1989; Nambu 2008; Saunders et al. 2015) (see model #1 in Fig. 1). The sum of literature is pointing to cortical areas in the frontal cortex. However, there is evidence that the globus pallidus as well as the thalamus directly project to areas in the posterior cortex (Finch et al. 1984). In addition, there are at least 3 different basal ganglia routes; one cortico-basal ganglia-cortical loop (Gritti et al. 1997; Vetrivelan et al. 2010; Saunders et al. 2015) and 2 cortico-basal ganglia-thalamo-cortical loops—the direct and the indirect loop (Nambu 2008; Saunders et al. 2015). To test whether one of these routes contribute significantly more to loss of consciousness, we modeled the cortico-basal ganglia-cortical loop and the cortico-basal ganglia-thalamo-cortical loop separately (Fig. 1, models #2 and #3, respectively). We note that it was not possible to further model the direct and indirect pathways within the cortico-basal ganglia-thalamo-cortical loop because of the low resolution of the functional data relative to the size of the internal and external segments of the globus pallidus. In addition, we included the model of recovery of consciousness by Schiff (2010) which does not assume a direct connection between the globus pallidus and cortical areas as well as from the posterior cingulate cortex to the striatum (model #4 in Fig. 1).

We also modeled additional possible alterations in connectivity that may occur during loss of consciousness. One assumption is that impairment of thalamic connectivity plays a significant role in impaired consciousness (Alkire et al. 2000; Laureys et al. 2000; Lull et al. 2010; Xie et al. 2011; Zhou et al. 2011; Laureys and Schiff 2012; Guldenmund et al. 2013; Baker et al. 2014) (model #2 in Fig. 1). However, Schiff (2010) emphasizes that these alterations may be due to impaired striatal inhibition of the globus pallidus which in turn has inhibitory effects on thalamo-cortical neuronal activity (models #5 and #6 in Fig. 1). Another region highly involved in alterations of consciousness after severe brain injury (Laureys et al. 1999; Fernández-Espejo et al. 2010; Vanhaudenhuyse et al. 2010; Crone et al. 2011, 2015), during sleep (Horovitz et al. 2008, 2009; Sämann et al. 2011), and during propofol-induced sedation (Fiset et al. 1999; Boly, Moran, et al. 2012; Monti et al. 2013) is the posterior cingulate cortex (model #7 in Fig. 1).

### Identification of Regions of Interest

To define the subcortical regions of interest in each subject (thalamus, caudate, putamen, and globus pallidus, separate for each hemisphere), the individual anatomical images were segmented using different cost functions (as implemented in FSL FIRST (Patenaude et al. 2011); see Lutkenhoff et al. (2015) for a detailed description of the method). To ensure quality, each participant's segmentations were visually inspected. In a next step, the segmentations of each hemisphere were combined and transformed into binary masks resulting in 3 masks for the subcortical areas (i.e., thalamus, striatum, and globus pallidus) for each participant (see Supplementary Fig. 1 for examples).

To select the region of interest within the medial frontal and parietal cortex, we used a different approach. Since most research regarding connectivity of the cortico-basal ganglia-thalamo-cortical loop has been performed in animals, the exact cortical locations in humans remain elusive. However, using the mean signal of a large area within the frontal and parietal cortices would be inappropriate when studying the effective dynamics within a network. Indeed, it is not only crucial to identify the cortical coordinates at the single-subject level, in order to account for inter-subject variability and to ensure functional connectivity to the subcortical areas of interest within each subject, but it is also crucial to identify the specific cortical subregions within cortex that share an independent common source of functional connectivity with all of the subcortical areas of interest, and thus, form a coherent network. Therefore, we have chosen an approach following the general idea by Di and Biswal (2014) in which a functionally connected network is identified to locate the exact regions of interest. Specifically, we performed a single-subject independent component analysis (ICA) as implemented in GIFT (the Group ICA of fMRI Toolbox; http://icatb.sourceforge.net/) as follows: (1) group ICA was performed within a mask comprising the 3 subcortical and all possible cortical regions of interest to estimate the number of components; (2) the analysis was rerun at the single-subject level using the estimated number of components; (3) the mean over all 4 conditions (to not bias the analysis) for each of the components were correlated with the subcortical masks; (4) all components associated with head motion, physiological noise, or cerebrospinal fluid fluctuations were excluded; (5) all components with high correlation were visually inspected to identify the component showing functional connectivity within the cortico-basal ganglia-thalamo-cortical loop; (6) the peak within each cortical region of interest was identified and we checked that similar areas within the medial frontal and parietal cortex were selected across subjects, that is, the medial prefrontal cortex and the ventral posterior cingulate cortex (BA 23) (see Supplementary Fig. 2 for examples); (7) for each subject, the first eigenvariates of the time series at the coordinates of both regions were extracted and used for further analyses. As mentioned above, this procedure ensures that the ensuing analysis is performed on cortical areas that are actually functionally connected within the cortico-basal ganglia-thalamo--cortical loop.

### Dynamic Causal Modeling

spDCM was performed as outlined below: (1) implementation of a general linear model (GLM); (2) extraction of BOLD fMRI time series for each subject and each condition; (3) specification of the model space (Fig. 1); (4) estimation of the specified models; (5) implementation of a Bayesian model selection routine to identify the "best" model; (6) comparison of the "best" model between conditions using the VBA toolbox. (7) Bayesian model averaging at the individual parameter level for all models in each subject and each condition.

DCM analyses were performed with the DCM12 routine implemented in SPM12 (Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/).

The general linear model (GLM) included the square, the temporal difference, the square of the differenced values of the 6 motion parameters, and outliers created by large motion to account for head motion and spin history, as well as the white matter and cerebrospinal fluid mean signals. In addition, the GLM contained an implicit high-pass filter of 1/100 Hz to remove possible ultraslow fluctuations due to hardware related drift.

To extract the BOLD fMRI time series in the 2 cortical areas, volumes of interest were defined as spheres with a radius of

8 mm centered at the individual coordinates of each subject. Note that the first eigenvariates were extracted after the GLM removing effects of head motion and low-frequency drift. For the 3 subcortical regions, the first eigenvariates of the BOLD fMRI time series in each individual subcortical mask were extracted.

Altogether, 7 models were tested across the 4 conditions (see Definition of Models). The connections between the 5 regions were specified as fixed connections in matrix A. Each model was fitted with an estimation procedure depending on the spectral densities over frequencies (complex cross spectra), that is, second-order statistics of the cross correlation of the time series (see Friston et al. 2014; Razi et al. 2015 for further details).

To determine the "best" model in each condition, we applied Bayesian model selection (Stephan et al. 2009). This approach does not assume group homogeneity meaning that it takes into account subject differences in the probability of a specific model generating the group data (equivalent to a random-effect analysis). Results of the Bayesian model selection procedure are shown as the protected exceedance probability (Rigoux et al. 2014) which uses the Bayesian omnibus risk (BOR) to compute a Bayesian model average of the exceedance probability, that is, the estimation of the likelihood of a particular model being the best compared with any other model given the group data. Using protected exceedance probability for inferences about specific models is more sophisticated since it takes into account that differences in model frequencies may be due to chance.

In the past, the possibility to compare model evidence across groups or conditions was very limited. A new approach recently introduced by Daunizeau et al. (2014) now allows one to test whether there is a significant difference between conditions (in terms of models) using the VBA toolbox. In a first step, we set up a model space of "tuples" encoding all combinations of models and conditions. Then, between-condition random-effects Bayesian model selection using families was performed to separate the tuples into 2 subsets, one in which the same models underlie all conditions, and another containing the remaining tuples. This way one can test whether the same model underlies all conditions. Similar in essence to an omnibus *F*-test and secondary condition-specific tests, we first implemented this method for all conditions to see whether the same model underlies all conditions. If the exceedance probability is very low (approximately 0), neither of the 2 families are more likely. This suggests that there are differences in the underlying "best" model between one or more conditions. In this case, we can test, similar to post hoc testing, the exact conditions which differ in their underlying models by applying the same method for only 2 conditions each.

To verify the robustness of our findings, we rerun the above described analyses (1) with a random selected subset of participants ($n = 12$), (2) with a reduced model space of 4 models (including only models #1, #3, #4, and #6), and (3) with an extended model space of 9 models including 2 additional models derived from model #1, in which the pallido-cortical connection is broken down into either a pallido-posterior cingulate connection (model #8; see lower panel in Supplementary Fig. 5) or a pallido-prefrontal connection (model #9; see lower panel in Supplementary Fig. 5).

Besides examining the difference in models between conditions in a qualitative sense, spDCM also allows to test for differences in individual parameters (effective connectivity, exponent and amplitude of neuronal fluctuations) in a quantitative sense. To exclude the possibility that between-conditions differences in estimated parameters may be due to differences in model fit, we performed fixed-effects Bayesian model averaging within each subject and each condition over the entire model space (Penny et al. 2010) and used the resulting parameters for classical inferences at the group-level. We performed one-way repeated-measures ANOVA permutation testing implemented in the ez library in R (www.R-project.org) using all parameters of intrinsic connectivity (BMS.DCM.rfx.bma.mEp.A) as well as the values of the amplitude and exponent of neuronal fluctuations (BMS.DCM.rfx.bma.mEp.a). Results of the repeated-measures ANOVA permutation tests were corrected for false-discovery rate to account for multiple comparisons (that is, 28 ANOVAs altogether). Post hoc tests (additionally corrected for false-discovery rate to account for multiple comparisons between conditions) were applied to all significant results.

## Results

### Bayesian Model Selection

Using Bayesian model selection (Stephan et al. 2009), 7 possible neuronal models of directed connectivity were compared (Fig. 1). The results show that model #1, which features the full cortico-subcortical loop including direct connections from the globus pallidus to the prefrontal and posterior cingulate cortices, best explains the data during wakefulness (Fig. 2). However, during loss of consciousness, none of the hypothesized models with impaired connectivity are likely given the data (models #2, #5, #6, and #7). Instead, loss of consciousness leads to a breakdown of pallido-cortical connections (model #3). After recovery from deep sedation, effective connectivity between the globus pallidus and the posterior cingulate cortex returns gradually (models #1 and #3).

### Comparisons of Connectivity Strength

To assess the role of individual connections, comparisons across conditions were also made at the parameter level. Findings at the parameter level reflect those using Bayesian model selection revealing significant reduction of connectivity strength of neuronal fluctuations between the globus pallidus and the posterior cingulate cortex during loss of consciousness (Fig. 3). Differences between conditions are significant in the connectivity strength from globus pallidus to posterior cingulate cortex ($P = 0.012$), from globus pallidus to thalamus ($P = 0.045$), and from striatum to globus pallidus ($P = 0.012$), computed with ANOVA permutation testing and corrected for false-discovery rate. Specific to loss of consciousness, the connectivity strength from the globus pallidus toward the posterior cingulate cortex shows a significant reduction (approaching zero). This goes along with a striatal disinhibition of the globus pallidus in both mild sedation and loss of consciousness. There is also a significant increase in the effective connectivity strength from the globus pallidus toward the thalamus after recovery compared with loss of consciousness (note that the difference compared with wake/sedation is only a trend and not significant). Moreover, there is a significant reduction between wake and loss of consciousness in the strength of the self-recurrent connectivity of the prefrontal cortex. The connectivity strength between globus pallidus and prefrontal cortex, however, does not appear to be modulated by loss of consciousness.

### Comparisons of Amplitude and Exponent of Neuronal Fluctuations

Finally, loss of consciousness was accompanied by a slowing of oscillations and a change in amplitude of the spectral density of neuronal fluctuations (Fig. 4). While there are significantly

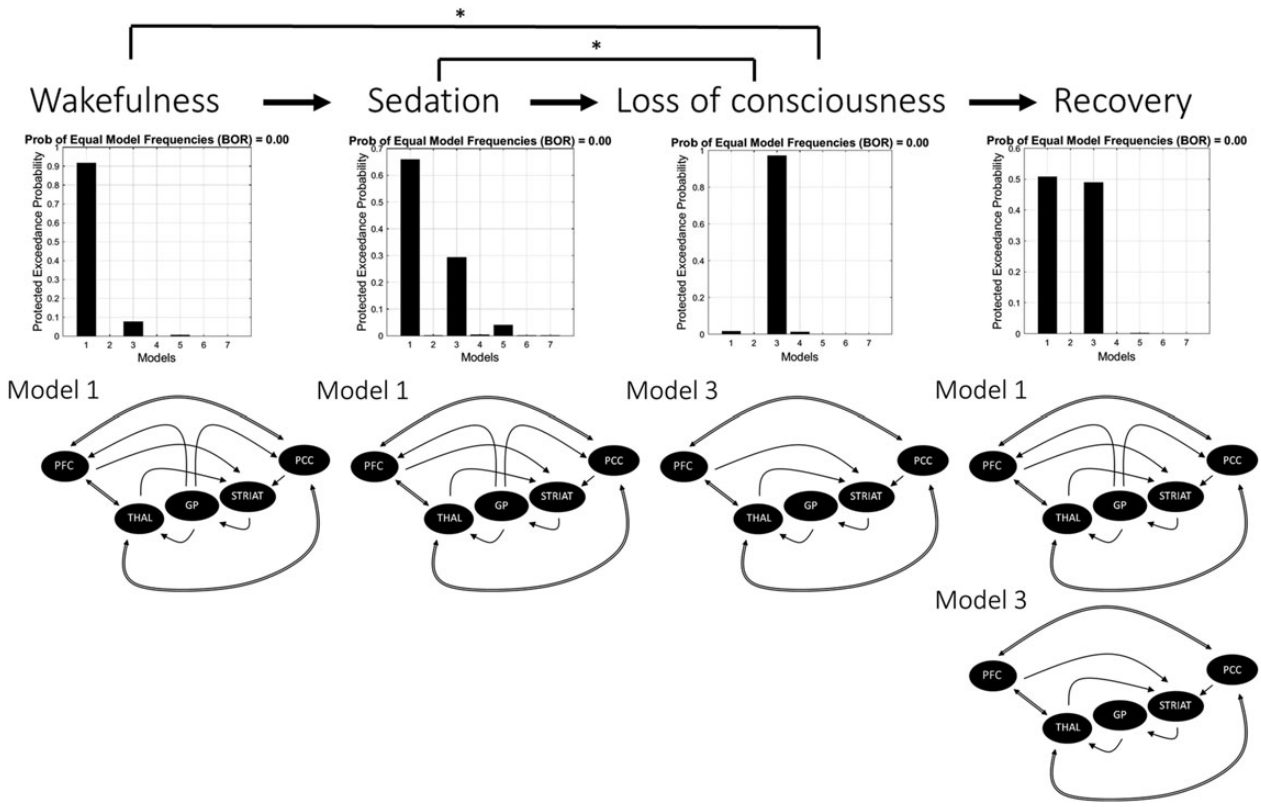


**Figure 2.** Results of the Bayesian model selection routine. The "best" model for each condition is shown. During loss of consciousness, efferent cortical connectivity from the globus pallidus fades and returns gradually after recovery from deep sedation. Significant differences in model evidence (indicated with asterisks) are present between wakefulness/sedation and loss of consciousness as computed with the VBA toolbox (Daunizeau et al. 2014). Model evidence is given as protected exceedance probability and BOR (Rigoux et al. 2014). PFC, prefrontal cortex; PCC, posterior cingulate cortex; GP, globus pallidus.

more low frequencies (Fig. 4A) in all regions during loss of consciousness (except in the posterior cingulate cortex) compared with all other conditions, the amplitude of neuronal fluctuations (Fig. 4B) is significantly weaker only in the globus pallidus. In the striatum, however, the amplitude is significantly stronger compared with wake and sedation.

### Validation of Findings

To further proof the robustness of findings, we assessed whether we can replicate the results when changing the parameters of the analysis. For this reason, we rerun all analyses at the model level with a subset of the data and different model spaces. As shown in Supplementary Figures 3–5, the main pattern of findings is robust. The model with a direct connection between globus pallidus and posterior cingulate cortex best fits the data during wakefulness. During loss of consciousness, the model that best fits the data does not have direct pallido-cortical connections. This finding was replicated when applying Bayesian model selection to a randomly selected subset of participants (see Supplementary Fig. 3), but also when decreasing the model space to 4 models (see Supplementary Fig. 4) or increasing the model space to 9 models (see Supplementary Fig. 5). Inference obtained by Bayesian model selection is relative to the model space. In other words, if you reduce or extend the model space, you change the posterior model probabilities (Stephan et al. 2009). Thus, replication of findings indicates a very strong effect. Interestingly, when modeling pallido-frontal and pallido-posterior connectivity separately, the model including only pallido-posterior connectivity explains the data best during wakefulness while, during recovery, the model with pallido-frontal connectivity is evaluated as very likely (Supplementary Fig. 5). The meaning of this finding will have to be investigated in future studies.

## Discussion

To evaluate the plausibility of various neuronal models of loss and recovery of consciousness, we investigated the effective connectivity of the cortico-basal ganglia-thalamo-cortical loop during transitions from wakefulness to propofol-induced unconsciousness and recovery using spectral dynamic causal modeling. Our findings indicate that, in the context of anesthesia, the breakdown of pallido-cortical connectivity within the cortico-basal ganglia-thalamo-cortical loop is the main factor characterizing the absence of consciousness. This "loss of consciousness" model (#3) appears to rise during sedation and remains elevated during recovery, confirming the dynamic shift of brain architecture of the posterior cingulate "hub" between different levels of consciousness.

Surprisingly, none of the hypothesized models of impaired consciousness as suggested by the current literature seem to fit the given data during transition to and out of unconsciousness. It is important to stress that we included only biologically and theoretically evidence-based models and that the winning model during wakefulness is the one combining all evidence from studies of the cortico-basal ganglia-thalamo-cortical loop as well as from studies of impaired consciousness in rodents and humans.

Contrary to popular models of loss and recovery of consciousness, we also find no evidence of a systematic association

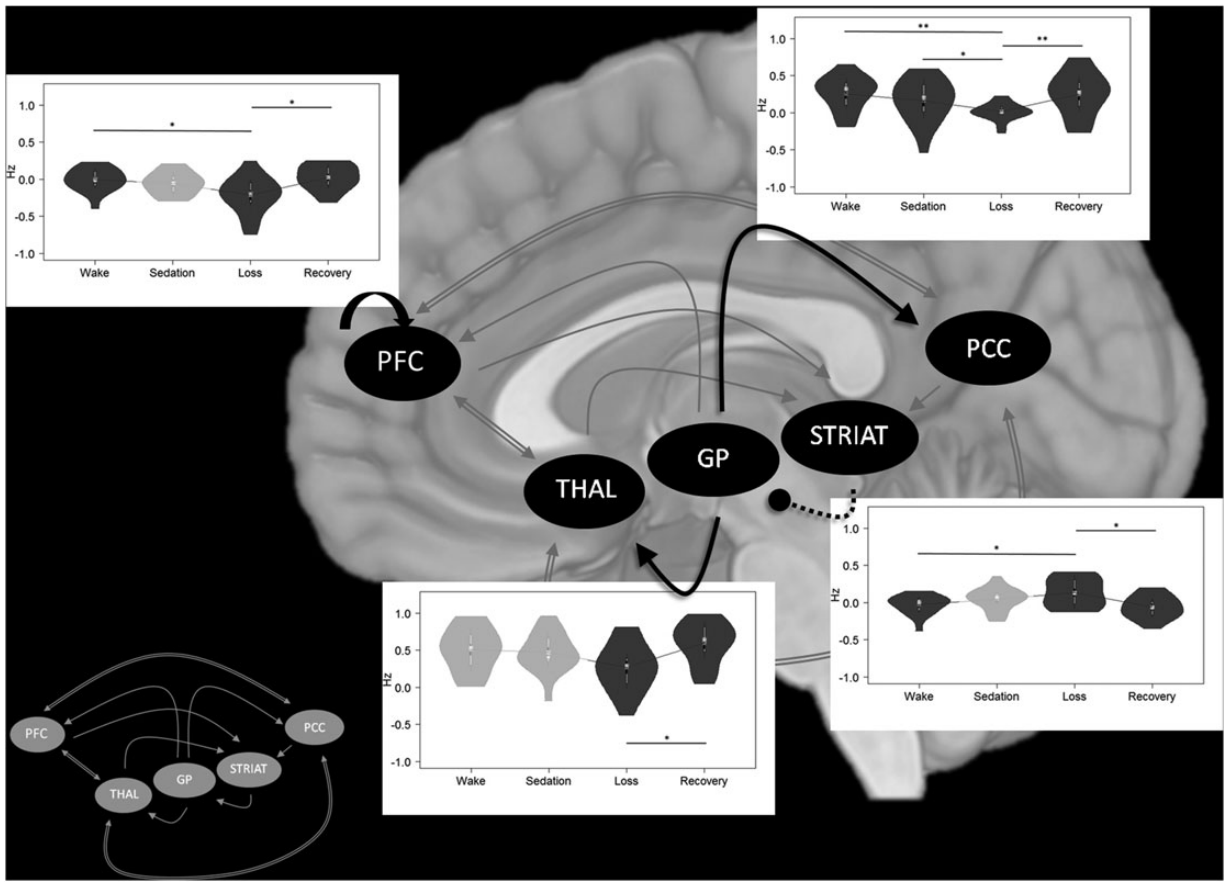


**Figure 3.** Changes in connectivity strength within the full cortico-basal ganglia-thalamo-cortical loop across levels of consciousness. One-way repeated-measures ANOVA permutation tests corrected for false-discovery rate with additional post hoc tests (also corrected for false-discovery rate) were computed for the resulting parameter estimates. Results reveal a significant loss of inhibition from the striatum (STRIAT) toward the globus pallidus (GP) for loss of consciousness compared with wakefulness and recovery of consciousness as well as a significant reduction of directed connectivity strength from the globus pallidus toward the posterior cingulate cortex (PCC) during loss of consciousness compared with all other conditions (wake; sedation; recovery). We also found a significant reduction of directed connectivity strength from the globus pallidus toward the thalamus (THAL) during loss of consciousness compared with recovery. Additionally, there was a significant reduction of self-recurrent connectivity strength during loss of consciousness compared with wakefulness and recovery in the prefrontal cortex (PFC). Asterisks indicate significant differences between conditions corrected for multiple comparisons (*$P < 0.05$; **$P < 0.01$). Dotted lines indicate an inhibitory influence of one region upon the other. Connectivity not significantly different across conditions is shown in light gray. A schematic representation of all connections included is shown in the lower left corner.

between loss of consciousness and thalamo-cortical (effective) connectivity in the context of anesthesia and thus confirm first indications from previously published work (Mhuircheartaigh et al. 2010; Silva et al. 2010; Boly, Perlbarg, et al. 2012; Monti et al. 2013). Nevertheless, this study is the first to show that a decrease of inhibitory influence from the striatum on the globus pallidus emerges during propofol-induced sedation and returns after recovery of consciousness. But instead of thalamo-cortical connectivity as hypothesized, the impact of the globus pallidus on the posterior cingulate cortex seems to be modulated by the level of consciousness. This aspect may be in line with the interpretation by Schiff (2010) that mechanisms influencing thalamo-cortical are related to higher cognitive functions and motor responsiveness after recovery of consciousness rather than to loss of consciousness itself.

Noteworthy, the breakdown of pallido-cortical connectivity strength is specific to the moment in which consciousness fades. This dynamic pattern of pallido-cortical connectivity (i.e., present during wakefulness and light sedation, breakdown during loss of consciousness, and returning during recovery of consciousness) may indicate that there is a certain threshold beyond which the direct pallidal modulation of the posterior cingulate cortex cannot be perpetuated and loss of consciousness emerges. In combination with the findings by Baker et al. (2014) implying that the transition to unconsciousness is initiated by subcortical mechanisms, our results highlight the significance of pallido-cortical connectivity in maintaining consciousness in humans.

As of a note, it may be somewhat unexpected that the findings at the parameter level do not completely replicate those at the model level in which emergence of the pallido-cortical connectivity during recovery is not as explicit. However, there is an important distinction between model comparison and comparison at the parameter level. A difference in models implies that one or more connections are absent in a quantitative sense, whereas a difference in the parameters (effective connectivity) suggests that the random effects of subjects are expressed qualitatively in terms of the connection strengths, under the assumption that the connection exists. The relation between emergence of consciousness and pallido-cortical connectivity may rather be due to the quality of connectivity.

The globus pallidus is part of the basal ganglia including multiple subcortical nuclei such as the putamen and the nucleus caudate. Growing literature highlights the prominent role of the

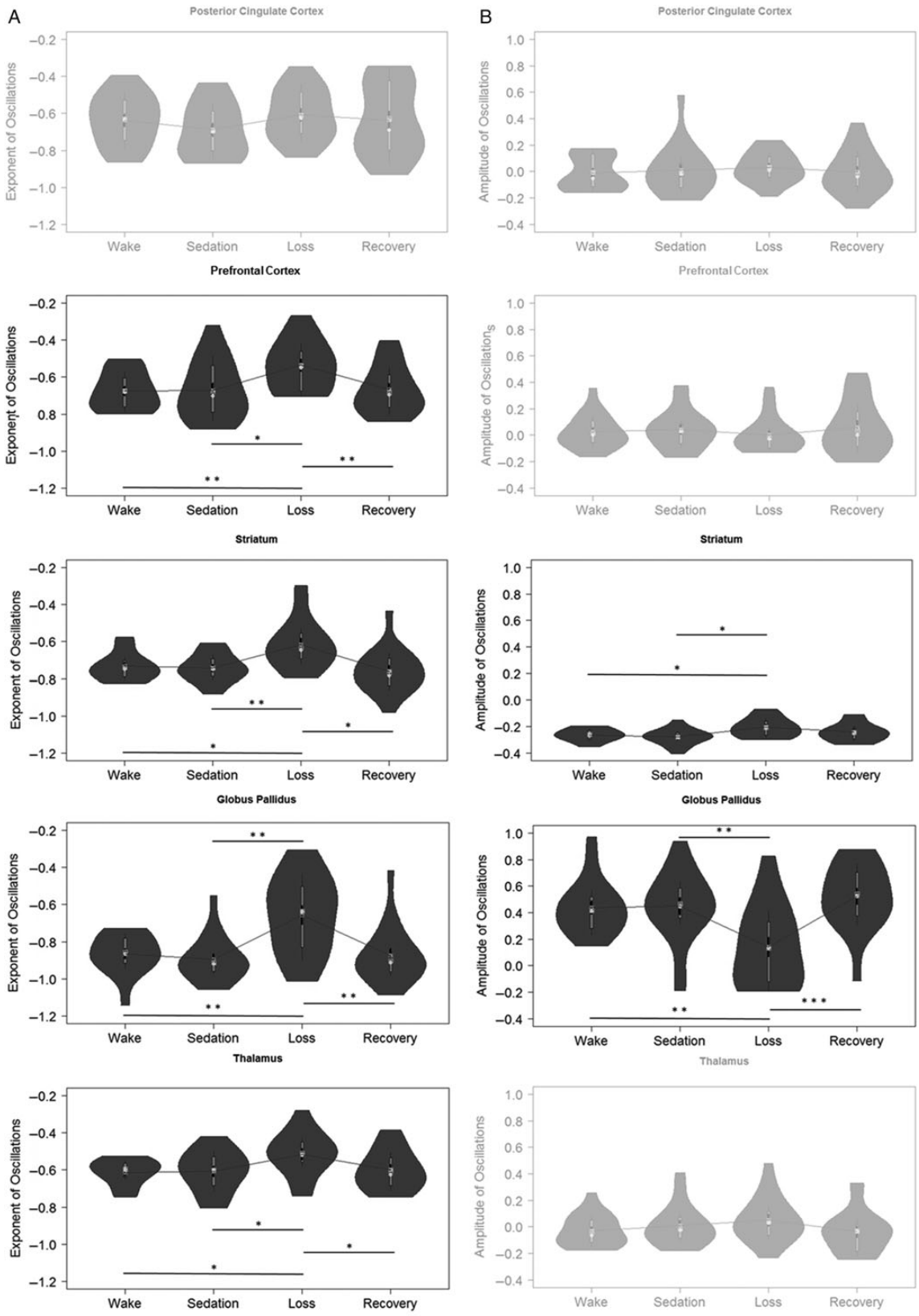


**Figure 4.** Exponent and amplitude of neuronal fluctuations in each region of the cortico-basal ganglia-thalamo-cortical loop. (*A*) Comparison of the exponent of neuronal fluctuations between conditions in each region. (*B*) Comparison of the amplitude of neuronal fluctuations between conditions in each region. Asterisks indicate significant differences between conditions (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). Regions with nonsignificant differences between conditions are shown in light gray.

basal ganglia in maintenance of behavioral responsiveness in animals (Qiu et al. 2010; Vetrivelan et al. 2010; Lazarus et al. 2012) and in humans (Mhuircheartaigh et al. 2010). Qiu et al. (2010) stress the importance of direct cortical projections from the globus pallidus because lesions to the thalamus do not affect cortical activity in the rodent model (Vanderwolf and Stewart 1988). In a large sample of 115 patients with disorders of consciousness, atrophy of the thalamus is inversely related only to motor behavior and communication while atrophy of the basal ganglia is inversely related to arousal and behavioral responsiveness as an indicator of the level of consciousness (Lutkenhoff et al. 2015).

Remarkably, loss of consciousness modulates the pallidal connectivity to the posterior cingulate cortex but has no significant effect on connectivity to the frontal cortex. Previous research in altered consciousness has demonstrated the central role of medial parietal regions after severe brain injury (Laureys et al. 1999; Fernández-Espejo et al. 2010; Vanhaudenhuyse et al. 2010; Crone et al. 2011, 2014, 2015), during sleep (Horovitz et al. 2008, 2009; Sämann et al. 2011) and during propofol-induced sedation (Boly, Moran, et al. 2012; Amico et al. 2014). The ventral part of the posterior cingulate cortex (BA 23) was chosen as a region of interest, because independent component analysis identified these coordinates as highly functionally connected with the chosen subcortical areas in each single subject. The ventral part of the posterior cingulate cortex is known to be involved in the regulation of the default mode network (Leech et al. 2011, 2012) which shows decreased connectivity during anesthesia (Greicius et al. 2008; Boveroux et al. 2010; Jordan et al. 2013). Collapsing input from the globus pallidus during loss of consciousness may have severe effects on the regulative functions of the ventral posterior cingulate cortex. The inability to maintain efficient control of the ventral posterior cingulate cortex, and thus, control of the default mode network, is associated with deficits in attention and cognition (Leech and Sharp 2014).

During loss of consciousness, oscillations of neuronal fluctuations became slower in all regions of the cortico-basal ganglia-thalamo-cortical loop (although not significant in the posterior cingulate cortex). In contrast, the amplitude of these oscillations decreased during loss of consciousness in the globus pallidus but increased in the striatum. It may be interesting to note that this pattern of oscillations, although a very different source of signal, is consistent with frequency analysis of electroencephalography data in propofol-induced sedation (Purdon et al. 2013), slow wave sleep (Greene and Frank 2010), and in patients with disorders of consciousness (Lehembre, Gosseries, et al. 2012). Delta frequencies, for example, typically have higher amplitudes than other frequency bands and delta power increases with severity of impaired consciousness, while power in the theta band decreases (Lehembre, Marie-Aurélie, et al. 2012).

In contrast to existing models of pallido-thalamic connectivity (Albin et al. 1989; Schiff 2010; Saunders et al. 2015), we observed an excitatory connectivity from the globus pallidus toward the thalamus. However, a substantial number of pallido-thalamic projecting neurons contain glutamate (Kha et al. 2000; Barroso-Chinea et al. 2008) and electrophysiological studies are inconsistent, suggesting the concomitant presence of excitatory and inhibitory transmission (Desiraju and Purpura 1969; Frigyesi and Machek 1970; Uno et al. 1978; Yamamoto et al. 1984).

It may seem arbitrary that pallidal inhibition during wakefulness results in stronger excitatory pallido-cortical connectivity compared with loss of consciousness during which there is no pallidal inhibition. However, the effects of the globus pallidus on the cortex are mediated by GABA and ACh involving diverse postsynaptic targets (Saunders et al. 2015). This complex interaction of direct and indirect pathways involved in basal ganglia connectivity and their multiple and possibly opposite influences on cortical excitability is not at least understood and still matter of present research (Calabresi et al. 2014). When interpreting the results, one should thus be mindful of the fact that some of the regions investigated are relatively small and might include subregions as well as different cell populations which add to the complexity of the connectivity patterns but cannot be fully captured by our technique.

Our results are representing the specific effects of propofol-induced loss and recovery of consciousness, and it is needless to say that the phenomenology of loss of consciousness is always intertwined with the mechanism employed to trigger the change in state, be it anesthetics, severe brain injury, deep sleep, or hypnosis. Nevertheless, a recent study comparing different causes of impaired consciousness (sleep and anesthesia) suggests that there is a common underlying neuronal mechanism to loss of consciousness independent of its trigger (Baker et al. 2014), at least with respect to the rodent brain. Furthermore, the design of our present study (that is, multiple recordings during light sedation, loss of consciousness, and recovery) allows us to directly assess the effects of propofol-induced loss of consciousness. The results do not reveal a significant difference in effective connectivity between the globus pallidus and the cortex in the condition “awake” (no exposure to propofol) compared with “sedation” (exposure to propofol) which would be expected if this study was solely observing a general effect of propofol instead of loss of consciousness.

A concern of dynamic causal modeling, which accounts for fMRI analyses of causal dynamics in general, is the indirect nature of fMRI BOLD and the underlying neuronal complexity which makes causal inference delicate. There is the need for strong and biological evaluated models, as well as a selection of nodes that are data driven on a single-subject basis. To address these concerns, we defined our models carefully based on biological knowledge and selected our regions of interest ensuring that the nodes are functionally connected in each single subject. Moreover, we varied several parameters to confirm that findings are robust. We used a subset of subjects to rerun the Bayesian model selection and we reduced as well as increased the model space. All changes revealed the same pattern of findings. Nevertheless, results are constrained by the finite selection of models and nodes compared.

## Conclusion

In this work, we directly compared various neuronal models of the cortico-basal ganglia-thalamo-cortical loop involved in consciousness by evaluating their plausibility to account for observed brain dynamics at different levels of consciousness. Our findings indicate that current models of impaired consciousness that focus on, for example, thalamo-cortical connectivity do not fit empirical data. Conversely, the inhibitory effects on thalamo-cortical neuronal activity due to striatal disinhibition of the globus pallidus seem, in fact, to be less distinguishing of the transition to unconsciousness and may be more related to recovery of cognitive functioning (see also Schiff 2010). Propofol-induced loss of consciousness, in contrast, appears to be mainly characterized by a breakdown in pallido-cortical connectivity driving the ventral posterior cingulate cortex. This study presents a novel, and most importantly, testable model of a core circuit for supporting consciousness. Future investigation needs to address the complex mechanisms of this circuit at a finer-grained level.

## Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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## Notes

*Conflict of Interest*. None declared.

## References

Adams JH, Graham DI, Jennett B. 2000. The neuropathology of the vegetative state after an acute brain insult. Brain. 123(Pt 7):1327–1338.

Albin RL, Young AB, Penney JB. 1989. The functional anatomy of basal ganglia disorders. Trends Neurosci. 12(10):366–375.

Alexander GE, DeLong MR, Strick PL. 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci. 9:357–381.

Alkire MT, Haier RJ, Fallon JH. 2000. Toward a unified theory of narcosis: Brain imaging evidence for a thalamocortical switch as the neurophysiologic basis of anesthetic-induced unconsciousness. Conscious Cogn. 9(3):370–386.

Amico E, Gomez F, Di Perri C, Vanhaudenhuyse A, Lesenfants D, Boveroux P, Bonhomme V, Brichant JF, Marinazzo D, Laureys S. 2014. Posterior cingulate cortex-related co-activation patterns: A resting state fmri study in propofol-induced loss of consciousness. PLoS One. 9(6):e100012.

Baars BJ. 2005. Global workspace theory of consciousness: Toward a cognitive neuroscience of human experience. Prog Brain Res. 150:45–53.

Baker R, Gent TC, Yang Q, Parker S, Vyssotski AL, Wisden W, Brickley SG, Franks NP. 2014. Altered activity in the central medial thalamus precedes changes in the neocortex during transitions into both sleep and propofol anesthesia. J Neurosci. 34(40):13326–13335.

Barroso-Chinea P, Rico AJ, Pérez-Manso M, Roda E, López IP, Luis-Ravelo D, Lanciego JL. 2008. Glutamatergic pallidothalamic projections and their implications in the pathophysiology of Parkinson's disease. Neurobiol Dis. 31(3):422–432.

Boly M, Moran R, Murphy M, Boveroux P, Bruno MA, Noirhomme Q, Ledoux D, Bonhomme V, Brichant JF, Tononi G, et al. 2012. Connectivity changes underlying spectral EEG changes during propofol-induced loss of consciousness. J Neurosci. 32(20): 7082–7090.

Boly M, Perlbarg V, Marrelec G, Schabus M, Laureys S, Doyon J, Pélégrini-Issac M, Maquet P, Benali H. 2012. Hierarchical clustering of brain activity during human nonrapid eye movement sleep. Proc Natl Acad Sci USA. 109(15):5856–5861.

Boly M, Seth AK, Wilke M, Ingmundson P, Baars B, Laureys S, Edelman DB, Tsuchiya N. 2013. Consciousness in humans and non-human animals: Recent advances and future directions. Front Psychol. 4:625.

Boveroux P, Vanhaudenhuyse A, Bruno MA, Noirhomme Q, Lauwick S, Luxen A, Degueldre C, Plenevaux A, Schnakers C, Phillips C, et al. 2010. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology. 113(5):1038–1053.

Calabresi P, Picconi B, Tozzi A, Ghiglieri V, Di Filippo M. 2014. Direct and indirect pathways of basal ganglia: a critical reappraisal. Nat Neurosci. 17(8):1022–1030.

Crone JS, Ladurner G, Höller Y, Golaszewski S, Trinka E, Kronbichler M. 2011. Deactivation of the default mode network as a marker of impaired consciousness: An FMRI study. PLoS One. 6(10):e26373.

Crone JS, Schurz M, Höller Y, Bergmann J, Monti M, Schmid E, Trinka E, Kronbichler M. 2015. Impaired consciousness is linked to changes in effective connectivity of the posterior cingulate cortex within the default mode network. Neuroimage. 110:101–109.

Crone JS, Soddu A, Höller Y, Vanhaudenhuyse A, Schurz M, Bergmann J, Schmid E, Trinka E, Laureys S, Kronbichler M. 2014. Altered network properties of the fronto-parietal network and the thalamus in impaired consciousness. Neuroimage Clin. 4:240–248.

Daunizeau J, Adam V, Rigoux L. 2014. VBA: a probabilistic treatment of nonlinear models for neurobiological and behavioural data. PLoS Comput Biol. 10(1):e1003441.

Dehaene S, Changeux JP. 2011. Experimental and theoretical approaches to conscious processing. Neuron. 70(2):200–227.

Dehaene S, Changeux JP. 2005. Ongoing spontaneous activity controls access to consciousness: A neuronal model for inattentional blindness. PLoS Biol. 3(5):e141.

Desiraju T, Purpura DP. 1969. Synaptic convergence of cerebellar and lenticular projections to thalamus. Brain Res. 15(2):544–547.

Di X, Biswal BB. 2014. Identifying the default mode network structure using dynamic causal modeling on resting-state functional magnetic resonance imaging. Neuroimage. 86: 53–59.

Fernández-Espejo D, Junque C, Cruse D, Bernabeu M, Roig-Rovira T, Fábregas N, Rivas E, Mercader JM. 2010. Combination of diffusion tensor and functional magnetic resonance imaging during recovery from the vegetative state. BMC Neurol. 10:77.

Finch DM, Derian EL, Babb TL. 1984. Afferent fibers to rat cingulate cortex. Exp Neurol. 83(3):468–485.

Fiset P, Paus T, Daloze T, Plourde G, Meuret P, Bonhomme V, Hajj-Ali N, Backman SB, Evans AC. 1999. Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study. J Neurosci. 19(13):5506–5513.

Frigyesi TL, Machek J. 1970. Basal ganglia-diencephalon synaptic relations in the cat. I. An intracellular study of dorsal thalamic neurons during capsular and basal ganglia stimulation. Brain Res. 20(2):201–217.

Friston KJ, Kahan J, Biswal B, Razi A. 2014. A DCM for resting state FMRI. Neuroimage. 94:396–407.

Greene RW, Frank MG. 2010. Slow wave activity during sleep: Functional and therapeutic implications. Neuroscientist. 16 (6):618–633.

Greicius MD, Kiviniemi V, Tervonen O, Vainionpää V, Alahuhta S, Reiss AL, Menon V. 2008. Persistent default-mode network connectivity during light sedation. Hum Brain Mapp. 29 (7):839–847.

Gritti I, Mainville L, Mancia M, Jones BE. 1997. GABAergic and other noncholinergic basal forebrain neurons, together with cholinergic neurons, project to the mesocortex and isocortex in the rat. J Comp Neurol. 383(2):163–177.

Guldenmund P, Demertzi A, Boveroux P, Boly M, Vanhaudenhuyse A, Bruno MA, Gosseries O, Noirhomme Q, Brichant JF, Bonhomme V, et al. 2013. Thalamus, brainstem and salience network connectivity changes during propofol-

induced sedation and unconsciousness. Brain Connect. 3(3):273–285.
Hannawi Y, Lindquist MA, Caffo BS, Sair HI, Stevens RD. 2015. Resting brain activity in disorders of consciousness: A systematic review and meta-analysis. Neurology. 84(12):1272–1280.
Horovitz SG, Braun AR, Carr WS, Picchioni D, Balkin TJ, Fukunaga M, Duyn JH. 2009. Decoupling of the brain's default mode network during deep sleep. Proc Natl Acad Sci USA. 106 (27):11376–11381.
Horovitz SG, Fukunaga M, de Zwart JA, van Gelderen P, Fulton SC, Balkin TJ, Duyn JH. 2008. Low frequency bold fluctuations during resting wakefulness and light sleep: A simultaneous EEG-FMRI study. Hum Brain Mapp. 29(6):671–682.
Jäntti V, Heikkinen E, Alahuhta S, Remes R, Suominen K. 2008. Cortical electroencephalogram from subcortical electrodes rather than electrosubcorticogram. Anesthesiology. 108 (5):963–964; author reply 964–965.
Jenkinson M, Bannister P, Brady M, Smith S. 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage. 17(2): 825–841.
Jordan D, Ilg R, Riedl V, Schorer A, Grimberg S, Neufang S, Omerovic A, Berger S, Untergehrer G, Preibisch C, et al. 2013. Simultaneous electroencephalographic and functional magnetic resonance imaging indicate impaired cortical top-down processing in association with anesthetic-induced unconsciousness. Anesthesiology. 119(5):1031–1042.
Kha HT, Finkelstein DI, Pow DV, Lawrence AJ, Horne MK. 2000. Study of projections from the entopeduncular nucleus to the thalamus of the rat. J Comp Neurol. 426(3):366–377.
Laureys S, Faymonville ME, Luxen A, Lamy M, Franck G, Maquet P. 2000. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. Lancet. 355(9217):1790–1791.
Laureys S, Lemaire C, Maquet P, Phillips C, Franck G. 1999. Cerebral metabolism during vegetative state and after recovery to consciousness. J Neurol Neurosurg Psychiatry. 67(1):121.
Laureys S, Schiff ND. 2012. Coma and consciousness: paradigms (re)framed by neuroimaging. Neuroimage. 61(2):478–491.
Lazarus M, Huang ZL, Lu J, Urade Y, Chen JF. 2012. How do the basal ganglia regulate sleep-wake behavior? Trends Neurosci. 35 (12):723–732.
Leech R, Braga R, Sharp DJ. 2012. Echoes of the brain within the posterior cingulate cortex. J Neurosci. 32(1):215–222.
Leech R, Kamourieh S, Beckmann CF, Sharp DJ. 2011. Fractionating the default mode network: Distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. J Neurosci. 31(9):3217–3224.
Leech R, Sharp DJ. 2014. The role of the posterior cingulate cortex in cognition and disease. Brain. 137(Pt 1):12–32.
Lehembre R, Gosseries O, Lugo Z, Jedidi Z, Chatelle C, Sadzot B, Laureys S, Noirhomme Q. 2012. Electrophysiological investigations of brain function in coma, vegetative and minimally conscious patients. Arch Ital Biol. 150(2–3):122–139.
Lehembre R, Marie-Aurélie B, Vanhaudenhuyse A, Chatelle C, Cologan V, Leclercq Y, Soddu A, Macq B, Laureys S, Noirhomme Q. 2012. Resting-state EEG study of comatose patients: a connectivity and frequency analysis to find differences between vegetative and minimally conscious states. Funct Neurol. 27(1):41–47.
Lull N, Noé E, Lull JJ, García-Panach J, Chirivella J, Ferri J, López-Aznar D, Sopena P, Robles M. 2010. Voxel-based statistical analysis of thalamic glucose metabolism in traumatic brain injury: Relationship with consciousness and cognition. Brain Inj. 24(9):1098–1107.
Lutkenhoff ES, Chiang J, Tshibanda L, Kamau E, Kirsch M, Pickard JD, Laureys S, Owen AM, Monti MM. 2015. Thalamic and extrathalamic mechanisms of consciousness after severe brain injury. Ann Neurol. 78(1):68–76.
Lutkenhoff ES, Rosenberg M, Chiang J, Zhang K, Pickard JD, Owen AM, Monti MM. 2014. Optimized brain extraction for pathological brains (optibet). PLoS One. 9(12):e115551.
MacDonald AA, Naci L, MacDonald PA, Owen AM. 2015. Anesthesia and neuroimaging: investigating the neural correlates of unconsciousness. Trends Cogn Sci. 19(2):100–107.
Mhuircheartaigh RN, Rosenorn-Lanng D, Wise R, Jbabdi S, Rogers R, Tracey I. 2010. Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: a functional magnetic resonance imaging study using propofol. J Neurosci. 30(27):9095–9102.
Monti MM, Lutkenhoff ES, Rubinov M, Boveroux P, Vanhaudenhuyse A, Gosseries O, Bruno MA, Noirhomme Q, Boly M, Laureys S. 2013. Dynamic change of global and local information processing in propofol-induced loss and recovery of consciousness. PLoS Comput Biol. 9(10):e1003271.
Nambu A. 2008. Seven problems on the basal ganglia. Curr Opin Neurobiol. 18(6):595–604.
Patenaude B, Smith SM, Kennedy DN, Jenkinson M. 2011. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage. 56(3):907–922.
Penny WD, Stephan KE, Daunizeau J, Rosa MJ, Friston KJ, Schofield TM, Leff AP. 2010. Comparing families of dynamic causal models. PLoS Comput Biol. 6(3):e1000709.
Purdon PL, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, Wong KF, Salazar-Gomez AF, Harrell PG, Sampson AL, Cimenser A, et al. 2013. Electroencephalogram signatures of loss and recovery of consciousness from propofol. Proc Natl Acad Sci USA. 110(12): E1142–E1151.
Qiu MH, Vetrivelan R, Fuller PM, Lu J. 2010. Basal ganglia control of sleep-wake behavior and cortical activation. Eur J Neurosci. 31 (3):499–507.
Ramsay MA, Savege TM, Simpson BR, Goodwin R. 1974. Controlled sedation with alphaxalone-alphadolone. Br Med J. 2(5920):656–659.
Razi A, Kahan J, Rees G, Friston KJ. 2015. Construct validation of a DCM for resting state FMRI. Neuroimage. 106:1–14.
Rigoux L, Stephan KE, Friston KJ, Daunizeau J. 2014. Bayesian model selection for group studies—revisited. Neuroimage. 84:971–985.
Rowe JB, Hughes LE, Barker RA, Owen AM. 2010. Dynamic causal modelling of effective connectivity from fMRI: are results reproducible and sensitive to Parkinson's disease and its treatment? Neuroimage. 52(3):1015–1026.
Sämann PG, Wehrle R, Hoehn D, Spoormaker VI, Peters H, Tully C, Holsboer F, Czisch M. 2011. Development of the brain's default mode network from wakefulness to slow wave sleep. Cereb Cortex. 21(9):2082–2093.
Saunders A, Oldenburg IA, Berezovskii VK, Johnson CA, Kingery ND, Elliott HL, Xie T, Gerfen CR, Sabatini BL. 2015. A direct GABAergic output from the basal ganglia to frontal cortex. Nature. 521(7550):85–89.
Schiff ND. 2008. Central thalamic contributions to arousal regulation and neurological disorders of consciousness. Ann N Y Acad Sci. 1129:105–118.
Schiff ND. 2010. Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci. 33(1):1–9.
Silva A, Cardoso-Cruz H, Silva F, Galhardo V, Antunes L. 2010. Comparison of anesthetic depth indexes based on thalamocortical local field potentials in rats. Anesthesiology. 112(2):355–363.

Song XX, Yu BW. 2015. Anesthetic effects of propofol in the healthy human brain: Functional imaging evidence. J Anesth. 29 (2):279–288.

Stephan KE, Penny WD, Daunizeau J, Moran RJ, Friston KJ. 2009. Bayesian model selection for group studies. Neuroimage. 46 (4):1004–1017.

Tononi G. 2010. Information integration: Its relevance to brain function and consciousness. Arch Ital Biol. 148(3):299–322.

Uno M, Ozawa N, Yoshida M. 1978. The mole of pallido-thalamic transmission investigated with intracellular recording from cat thalamus. Exp Brain Res. 33(3–4):493–507.

Vanderwolf CH, Stewart DJ. 1988. Thalamic control of neocortical activation: a critical re-evaluation. Brain Res Bull. 20(4):529–538.

Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJ, Bruno MA, Boveroux P, Schnakers C, Soddu A, Perlbarg V, Ledoux D, Brichant JF, et al. 2010. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain. 133(Pt 1):161–171.

Velly LJ, Rey MF, Bruder NJ, Gouvitsos FA, Witjas T, Regis JM, Peragut JC, Gouin FM. 2007. Differential dynamic of action on cortical and subcortical structures of anesthetic agents during induction of anesthesia. Anesthesiology. 107 (2):202–212.

Vetrivelan R, Qiu MH, Chang C, Lu J. 2010. Role of basal ganglia in sleep-wake regulation: neural circuitry and clinical significance. Front Neuroanat. 4:145.

Xie G, Deschamps A, Backman SB, Fiset P, Chartrand D, Dagher A, Plourde G. 2011. Critical involvement of the thalamus and precuneus during restoration of consciousness with physostigmine in humans during propofol anaesthesia: a positron emission tomography study. Br J Anaesth. 106 (4):548–557.

Yamamoto T, Noda T, Miyata M, Nishimura Y. 1984. Electrophysiological and morphological studies on thalamic neurons receiving entopedunculo- and cerebello-thalamic projections in the cat. Brain Res. 301(2):231–242.

Zhou J, Liu X, Song W, Yang Y, Zhao Z, Ling F, Hudetz AG, Li SJ. 2011. Specific and nonspecific thalamocortical functional connectivity in normal and vegetative states. Conscious Cogn. 20(2):257–268.