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Relating neural oscillations to laminar fMRI connectivity in visual cortex

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Laminar functional magnetic resonance imaging (fMRI) holds the potential to study connectivity at the laminar level in humans. Here we analyze simultaneously recorded electroencephalography (EEG) and high-resolution fMRI data to investigate how EEG power modulations, induced by a task with an attentional component, relate to changes in fMRI laminar connectivity between and within brain regions in visual cortex. Our results indicate that our task-induced decrease in beta power relates to an increase in deep-to-deep layer coupling between regions and to an increase in deep/middle-to-superficial layer connectivity within brain regions. The attention-related alpha power decrease predominantly relates to reduced connectivity between deep and superficial layers within brain regions, since, unlike beta power, alpha power was found to be positively correlated to connectivity. We observed no strong relation between laminar connectivity and gamma band oscillations. These results indicate that especially beta band, and to a lesser extent, alpha band oscillations relate to laminar-specific fMRI connectivity. The differential effects for alpha and beta bands indicate that they relate to different feedback-related neural processes that are differentially expressed in intra-region laminar fMRI-based connectivity.

Key words: laminar-fMRI; connectivity; EEG; neural oscillations.

Introduction

Investigating directional laminar connectivity during task conditions has so far remained primarily the domain of invasive electrophysiological investigations in animals (van Kerkoerle et al. 2014). Over the past decade, the development of high-resolution functional magnetic resonance imaging (fMRI) has made it possible to measure laminar level activity in humans noninvasively (Koopmans et al. 2010; Polimeni et al. 2010; Siero et al. 2011; Muckli et al. 2015; Kok et al. 2016; Huber et al. 2017; Lawrence et al. 2018; Finn et al. 2019; Sharoh et al. 2019). Laminar-specific anatomical connections directly relate to feedforward and feedback projections between regions at different levels in the cortical hierarchy (Douglas and Martin 2004; Markov and Kennedy 2013). These projections have been related to frequency-specific directional connectivity derived from electrophysiological measures. Recently, Sharoh et al. (2019) demonstrated that laminar-specific feedforward and feedback connections of the visual word form area with other regions can be studied with cortical depth-resolved fMRI. Since frequency-specific

electrophysiological synchronization has been directly related to laminar-specific feedforward and feedback projections, this raises the question of how frequency-specific neural synchronization relates to laminar level fMRI connectivity (Scheeringa and Fries 2019). Several frameworks for cortical processing explicitly link frequency-specific neural synchronization to laminar-specific feedforward and feedback projections between brain regions (Bastos et al. 2012; Fries 2015; Bonnefond et al. 2017). Laminar level fMRI connectivity could provide a unique opportunity to study such feedforward and feedback projections noninvasively in humans that can contribute to testing theoretical frameworks like these. For this, it is essential to first establish how neural oscillations in separate frequency bands relate to laminar connectivity. In an exploratory re-analysis of simultaneously recorded laminar fMRI-electroencephalography (EEG) data during an attention-demanding task (Scheeringa et al. 2016), we therefore investigate how modulations of neural oscillations relate to changes in connectivity between regions in the early visual cortex.

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Invasive recordings in animals have linked feedforward connectivity to inter-regional synchronization in the gamma and theta bands, while feedback has been linked to alpha and beta band synchronization (Bastos et al. 2012; Bosman et al. 2012; van Kerkoerle et al. 2014; Bastos et al. 2015). Anatomically, these gamma/theta band feedforward connections are thought to originate from superficial (layers II/III) in lower order regions and target mainly middle layers (layer IV) in higher order regions. Feedback-related alpha and beta band activity is thought to be conveyed from deep layers in higher order regions (layers V/VI) (Buffalo et al. 2011; van Kerkoerle et al. 2014; Fries 2015) to layers outside layer IV in lower order regions, although for nearby regions feedback connections between superficial layers (layers II/III) have also been identified (Markov et al. 2013). Although true anatomical layers can at the moment not be uniquely identified and measured with high-resolution fMRI, the sub-millimeter resolution that can now be achieved does allow for depth-resolved measures of the hemodynamic response (roughly 3–4 independent observations over the width of the cortex) at a similar spatial scale to the underlying 3 cortical “super” layers defined as infragranular, supragranular, and granular. Laminar fMRI therefore allows us to study connectivity between various cortical depths noninvasively (Huber et al. 2017; Wu et al. 2018; Sharoh et al. 2019; Huber et al. 2020), and when combined with electrophysiological measures like EEG, we can relate these effects to frequency-specific neural synchronization. Here we implemented this combination by first computing individual task effects in cortical depth-dependent correlation-based connectivity. Subsequently, we correlated this task effect over subjects with task effects in frequency-specific EEG power bands. We chose here to use channel level power and not connectivity measures like source level coherence or granger causality (Bastos and Schoffelen 2015), since our setup with only 64 electrodes measured inside the MRI environment does not allow for adequate source separation for the regions in early visual cortex under investigation here. From previous research using MEG and EEG, we know the alpha, beta, and gamma power effects originate from early visual cortex (Hoogenboom et al. 2006; Fries et al. 2008; Muthukumaraswamy and Singh 2013). Based on these results, we consider our EEG power measures to reflect neural synchronization across regions in the early visual cortex.

In the original analyses of the data used here (Scheeringa et al. 2016), we demonstrated that the alpha, beta, and gamma band effects observed in this task correlated to the blood oxygenation level-dependent (BOLD) effect in different cortical layers in early visual cortex (V1, V2, and V3). Alpha oscillations were found to correlate negatively with both deep and superficial layers, while beta oscillations were found to correlate negatively only with deep layer BOLD. For the gamma band, a positive correlation was found in middle and superficial layers. These findings were largely in line with

the likely laminar origins and function of these rhythms, suggesting a link between laminar BOLD and neural synchrony-related feedforward and feedback projections between brain regions (van Kerkoerle et al. 2014; Bastos et al. 2015). Crucially, the experimental paradigm task included a crude attention manipulation (attention ON versus Attention OFF; see Fig. 1A) that forms the basis for the present contribution. Recent publications on laminar fMRI have demonstrated the possibility of performing laminar level fMRI connectivity analyses (Sharoh et al. 2019; Huber et al. 2020) for both intra- and inter-regional connectivity. This led us to revisit our previously recorded data in order to explore whether not only laminar-specific BOLD amplitude but also laminar fMRI connectivity relates to frequency-specific EEG power. Specifically, by correlating task effects in laminar connectivity within and between regions in the visual cortex (V1, V2, V3), with task effects in alpha, beta, and gamma bands (see Fig. 1B and C for the original findings for this task contrast).

The results from the new analyses presented here should be interpreted as an exploration of how laminar fMRI-based estimates of inter- and intra-regional coupling relate to neural oscillations. We chose a paradigm that was known from previous studies using MEG and EEG (Hoogenboom et al. 2006; Hoogenboom et al. 2010; Muthukumaraswamy and Singh 2013) to induce changes in multiple frequency bands in the early visual cortex. Furthermore, the EEG responses are highly similar to those invasively recorded in animals from visual regions in tasks investigating selective attention (Fries et al. 2008). Together, this gives us confidence that the signals we measure originate from early visual cortex, although the source location cannot be accurately be estimated from our data due to the relatively low number of channels and the larger spatial imprecision of EEG compared to MEG and intracranial recordings. The crude task modulation added to the paradigm (attention On vs. Off) was introduced in the first place to induce meaningful variation over subjects in task effects across the frequency bands modulated by the visual stimulation, as well as across all layers of the cortex. It was not intended to investigate specific individual processes such as prediction, attention, or arousal. In this study, we make use of the variation in task effect over subjects, by correlating the task effects in alpha, beta, and gamma band power to the task effects in measures of inter- and intra-regional coupling over subjects.

The frequencies investigated have been previously directly linked to specific processes (Klimesch et al. 2007; Jensen and Mazaheri 2010; Bastos et al. 2012; Fries 2015). Within paradigms addressing selective attention and prediction, gamma band oscillations are predominantly observed in the superficial layers and have been associated with attention modulated gain of the feedforward stream (Bosman et al. 2012; Roberts et al. 2013; Bastos et al. 2015; Fries 2015; Michalareas et al. 2016) and, within a predictive coding framework, the feedforward

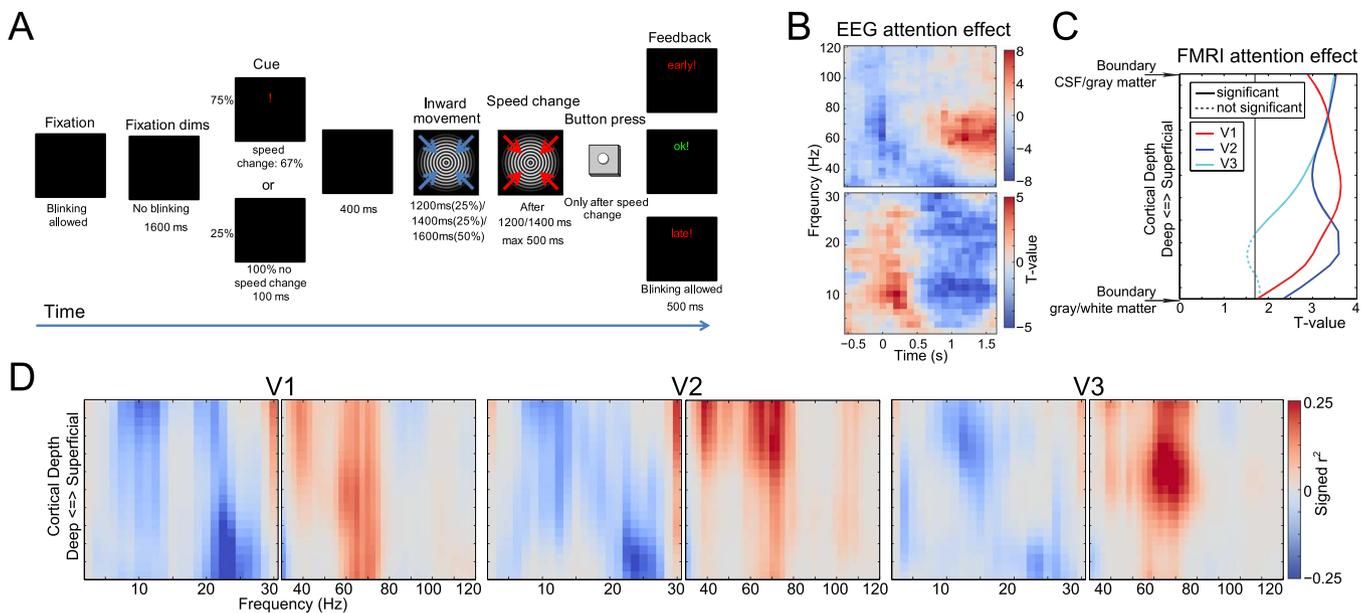


Fig. 1. Experimental paradigm and attention effects. A) Schematic representation of a trial of the experimental paradigm. Subjects were instructed to focus on a fixation dot that would dim 1,000 ms before trial onset and indicated that subjects were not to blink anymore. At the trial onset, subjects would see a cue for 100 ms indicating whether a speed increase in the inward contractions of the grating would likely occur (75% of the trials) or certainly not occur (25% of the trials). If so, these changes would start 500 ms after the onset of the cue. If a speed change was cued, it would occur in 67% of the trials and not occur in 33% of the trials. The trials where a speed increase was cued but did not occur (attention ON condition) and the trials where the cue indicated a speed change would definitely not occur (attention OFF condition) are the basis of the work presented here (attention contrast). B) Time–frequency representation of the t -values for the attention contrast in EEG power, which was computed as the log-transformed ratio of the power in both conditions. For each time–frequency point, the effect was calculated as the \log_{10} of the ratio between the attention ON and OFF conditions. Time is relative to the onset of visual stimulation. C) T -values across the cortical depth of the cortex for the attention contrast for the cortical depth-resolved BOLD signal for V1, V2, and V3. The BOLD signal was estimated for 21 points across the width of the cortex, where the boundary between CSF and gray matter coincides with the left limit of the plot and the border between gray and white matter with the right limit. D) Signed square correlation between the attention effect in the EEG power averaged over 0.6–1.6 s during the visual stimulation and the attention effect in depth-resolved BOLD signal for V1, V2, V3. Here, the boundary between CSF and gray matter coincides with the top of the y-axis and the border between gray and white matter with the bottom of the y-axis. Frequency is plotted on the x-axis, separately for low (<30 Hz) and high (40–120 Hz) frequencies due to the difference in the ranges of the frequency smoothing for the 2 frequency ranges (<30 Hz): ± 2.5 Hz; 30–120 Hz: ± 10 Hz. The results depicted in B–D were previously reported in Scheeringa et al. (2016) and all panels were adapted from this previous work.

projection of prediction errors (Bastos et al. 2012; Bastos et al. 2020). Within this framework, alpha/beta oscillations are thought to reflect feedback projections that carry predictions from higher order to lower order regions (Bastos et al. 2012; Bastos et al. 2020). Others have associated alpha and beta oscillations with inhibition of task irrelevant regions whose activity could otherwise interfere with task performance (Klimesch et al. 2007; Jensen and Mazaheri 2010; Zumer et al. 2014). All these perspectives explicitly or implicitly rely on (changes in) laminar-specific neural coupling within and between brain regions. Laminar-level fMRI connectivity holds the unique key to measure such coupling noninvasively in humans (Scheeringa and Fries 2019). The present work links laminar fMRI connectivity to such neural oscillation-based models of cognitive brain function in 2 ways. First, we shed light on whether laminar fMRI-based connectivity (either alone or combined with EEG) can be used to address processes traditionally investigated with invasive electrophysiology. Second, the presence (or absence) of a relation between laminar connectivity (measured by fMRI) and neural oscillations (measured by EEG) is relevant for cognitive models that predict specific roles for neural oscillations in relation to laminar level coupling within and between brain regions.

Materials and methods

The full preprocessing analysis pipeline for the data is described in our earlier work (Scheeringa et al. 2016). Here we only repeat parts that are relevant for the additional analyses presented here.

Data and code availability

This study was based on existing dataset published in Scheeringa et al. (2016). The data and code for this original dataset is available through the Donders Repository (<https://doi.org/10.34973/rzrzr-2b58>). The original code and data of the current study is also available through the Donders Repository (<https://doi.org/10.34973/qzx7-et46>).

Subjects

In this article, we analyzed the data of the same 30 subjects that were included in the analysis of our earlier work (26 female, 4 male, age 18–26 years) out of originally 34 subjects (29 female, 5 male). Four subjects were excluded due to poor EEG quality. These subjects participated in 3 blocks of an attention-demanding visual task inside a 3T MRI scanner while simultaneously EEG, high-resolution fMRI, eye movements, and pupil size were measured. Before taking part in the experiment, written

informed consent was obtained from the subjects. The experiment was approved by a local ethical committee (CMO Arnhem/Nijmegen region). For one of the included subjects, only 2 blocks were carried out.

Experimental paradigm

The details of the experimental paradigm and procedure are described in detail in [Scheeringa et al. \(2016\)](#). A schematic overview is depicted in [Fig. 1A](#). In short, subjects were required to fixate on a central fixation point, while simultaneously a circular inward contracting grating was presented for up to 1,600 ms. Their task was to respond with a button press as soon as the speed of the contraction increased. Crucial for the analyses presented here, a cue indicated whether this was likely to happen (75% of the trials, 67% cue validity) or would not happen at all (25% of the trials, 100% cue-validity). The analysis presented here pertains to the 2 conditions where no button-press was required; the “attention ON” condition where a speed change was cued but did not occur, and the “attention OFF” condition where no speed change was cued. This task was chosen since it reliably induces decreases in alpha and beta power and increases in gamma power. Except for one subject who stopped the measurement prematurely, all subjects performed 3 blocks of the task. Within each block, there were 18 trials for both the attention ON condition without a speed change and the attention OFF condition. This paradigm and task manipulation were chosen because they induce decreases in alpha and beta EEG power and increases in gamma band power relative to baseline, as well as in the attention ON condition compared to the attention OFF condition. This allows us to investigate the relationship of oscillatory power in different frequency ranges with laminar level BOLD activity ([Scheeringa et al. 2016](#)) and connectivity (presented here) in the same task. As a consequence, our task modulation was not a clean modulation of attention and should not be interpreted as such, since relevant cognitive processes like arousal and the predictability of the speed change differed between the conditions.

Preprocessing

Here, we describe briefly the preprocessing steps from our previous work ([Scheeringa et al. 2016](#)) that are relevant to the understanding of the new analyses and results presented here.

EEG was recorded together with high-resolution fMRI. In order to obtain high-quality estimates of the frequency-specific EEG power responses to the task, we used an ICA denoising strategy ([Debener et al. 2006](#)) that projects the denoised data back to channel level. The EEG data used for relating power to laminar fMRI (here connectivity, in our previous work activity) were averaged over a subset of the channels reflecting the strongest effect after this denoising step. Our previous analysis confirmed strong power decreases from baseline in alpha and beta bands and increases in the gamma

band. Crucial for the analyses presented here, in the last second of the trial, alpha and beta power was lower for the attention ON condition compared to the attention OFF condition while gamma power was higher in this condition ([Fig. 1B](#)).

From the high-resolution fMRI data, we estimated the BOLD signal at 21 depths from the boundary between white and gray matter to the boundary between gray matter and cerebrospinal fluid (CSF) obtained from a high-resolution co-registered T1 anatomical scan. These estimated boundaries consisted of triangulated meshes, where each vertex in the mesh delineating CSF from gray matter was matched with a vertex in the mesh delineating gray matter and white matter. The 21 estimated cortical depths were estimated between these vertex pairs using nearest neighbor interpolation. Since layers in cortex preserve relative volume (and not thickness) across changes in curvature ([Bok 1929](#)), data points for which data were interpolated were spaced accounting for this property. Our fMRI data were recorded with a resolution of 0.8 mm isotropic. This gives roughly 3–4 independent measures across the depth of the cortex. With our interpolation, we therefore oversample this with roughly a factor of 5–6. For the subsequent analyses, we selected the vertex pairs that were most activated irrespective of attention condition for each bin within V1, V2, and V3 in both hemispheres separately. These visual regions were determined based on retinotopic mapping.

For the main analysis presented here, we selected the top 10% activated vertex pairs. Although arbitrary, averaging over task activated parts within the 6 visual regions obtained from retinotopic mapping (left and right hemisphere V1, V2, and V3) is necessary to increase the signal-to-noise level, which is very low for the high-resolution individual voxels. For this, we first calculated the *t*-values related to visual stimulation irrespective of attention condition for all data points between vertex pairs by means of nearest neighbor interpolation from the effects calculated for each voxel. Subsequently, the *t*-values between vertex pairs were averaged with the exclusion of the 5 most superficial depth bins to avoid effects from pial veins. Within each region, we then selected the 10% vertex pairs with the highest average *t*-value.

For the 3 regions, BOLD was observed to be higher in the attention ON condition across all cortical depths ([Fig. 1C](#)). Besides these attention effects in EEG power and BOLD, we also observed that the pupil size was larger during the last second of the trial during attention ON ([Supplementary Fig. S1](#)). In our previous analyses, we repeated the integrated EEG-fMRI analyses for the top 5% and 25% activated vertices to verify whether the arbitrary choice of the threshold affected the results, which is also performed in the present study.

Analysis rationale

Most commonly used connectivity measures condense a series of measurements (e.g. time series data) into a

single value (e.g. correlation, regression slopes, coherence, granger causality). Such a single value can therefore not be related to other variables (e.g. EEG signals) over time. We therefore calculate a correlation over subjects between subject-specific fMRI connectivity measures and their EEG power counterparts. In summary: For each individual subject's fMRI data, we calculate the connectivity between the signals of 2 layers, separately for both the "attention ON" and "attention OFF" conditions. These 2 layers can be in the same region or in different regions (Fig. 3). We calculate a difference score for attention ON and OFF, which is then taken as the attention effect in connectivity for that particular combination of layers and regions and, importantly, for that specific subject. To establish the link with the EEG frequency bands, we subsequently assess the correlation across subjects of this subject-specific fMRI attention contrast value with the subject-specific attention effects in the EEG power for each frequency band. So, functional connectivity is assessed at the subject level (i.e. one value per subject), whereas EEG and fMRI are linked at the group level. The above is repeated for all possible combinations of layers and regions.

Estimating laminar connectivity

In this study, we estimate task-related laminar fMRI connectivity from single-trial BOLD amplitude estimates for all region/cortical depth combinations of the 6 regions involved. This was carried out by fitting the canonical HRF as implemented in SPM 12 (<https://www.fil.ion.ucl.ac.uk/spm/>) for every trial of the attention OFF and attention ON (without an increase in contraction speed) conditions, using multiple linear regression. For each trial of these 2 conditions, a single regressor was constructed by convolving a mini block of 1,600 ms representing the visual stimulation part of the trial with the canonical HRF. The parameter (beta) estimates for these regressors therefore provide estimates of the single-trial BOLD response for each trial. Within the context of the regression model, the other 2 conditions (trials with speed change after 1,200 ms and 1,400 ms) were each modeled by one regressor and included as confound regressors. The other confound regressors included were (i) 2 regressors modeling the button presses in the 2 trial types with a speed change; (ii) 2 regressors modeling the reaction time as a parametric modulation (one for each trial type with a speed change); (iii) regressors modeling the behaviorally incorrect trials for the 2 conditions with a speed change; (iv) the realignment parameters, their squares, and derivatives to control for possible movement artifacts; (v) a regressor modeling the T1 effect related to the pause after every third scan; and (vi) 6 sine and 6 cosine waves with frequencies up to 0.006 Hz. We subsequently correlated for each layer condition the beta/parameter estimates of for every layer region/layer combination in every block for every subject. For the computation of this correlation, erroneous trials and

trials including eye blinks were excluded. As a consequence, on average 4.0% of the trials (range 0%–14.8%) were excluded. Subsequently, a Fisher z-transformation was applied to the correlations to account for the ceiling effects in correlation values. These values were then averaged over the task blocks and the specific region combinations within a grouping. For the main analysis, we grouped combinations into intraregional and interregional connectivity. For intraregional connectivity, connectivity was averaged over connectivity within V1, V2, and V3 regions in both hemispheres. For interregional connectivity, we averaged over V1-V2, V1-V3, and V2-V3 combinations in both hemispheres. To complement the main analyses, the intraregional connectivity of V1, V2, V3 separately and between V1, V2, and V3 were also analyzed (averaged over both hemispheres). These groupings are depicted in the first column (panels A and E) of Fig. 3. The effect of the attention manipulation was calculated as the difference between the attention ON and the attention OFF estimate of laminar connectivity for these groupings. This attention effect was subsequently used to correlate over subjects with the attention effects in alpha, beta, and gamma power and in pupil size. Significant attention effects in laminar connectivity were tested using a nonparametric cluster-based permutation test (Maris and Oostenveld 2007) implemented in Fieldtrip (Oostenveld et al. 2011) for which the details are described in Scheeringa et al. (2016). Clusters were defined by layer-by-layer combination for which $P < 0.05$ uncorrected (2-tailed). We used 200,000 permutations to estimate the reference distribution of cluster-sums.

Correlating laminar connectivity with EEG power and pupil size

We correlated the attention effects in the alpha (7.5–12.5 Hz), beta (21.25–27.5 Hz), and gamma (50–80 Hz) bands, and the attention effect we observed in pupil size with the attention effects in laminar intra- and intraregional connectivity (Fig. 3A and E). In addition, we applied the same approach as a supplementary analysis to the underlying individual region combinations. Laminar connectivity and EEG power measures themselves are potentially influenced by non-neuronal variables that vary over subjects like heart rate, local blood flow and local vasculature (laminar fMRI), and brain size, skull thickness, and residual EMG (EEG). By correlating the attention effects in both modalities over subjects and not the raw measures we correct for these effects insofar, these are not modulated by our attention modulation. For the frequency bands mentioned above, we averaged over the attention effect, expressed as a log ratio of the attention-on versus attention-off condition, over all time bins from 500 ms until 1,600 ms after the onset of visual stimulation and all frequency bins within the indicated ranges. For the pupil size, the log-ratio of the attention effect in pupil size was averaged over the same time period. The partial Spearman correlation (assuming a

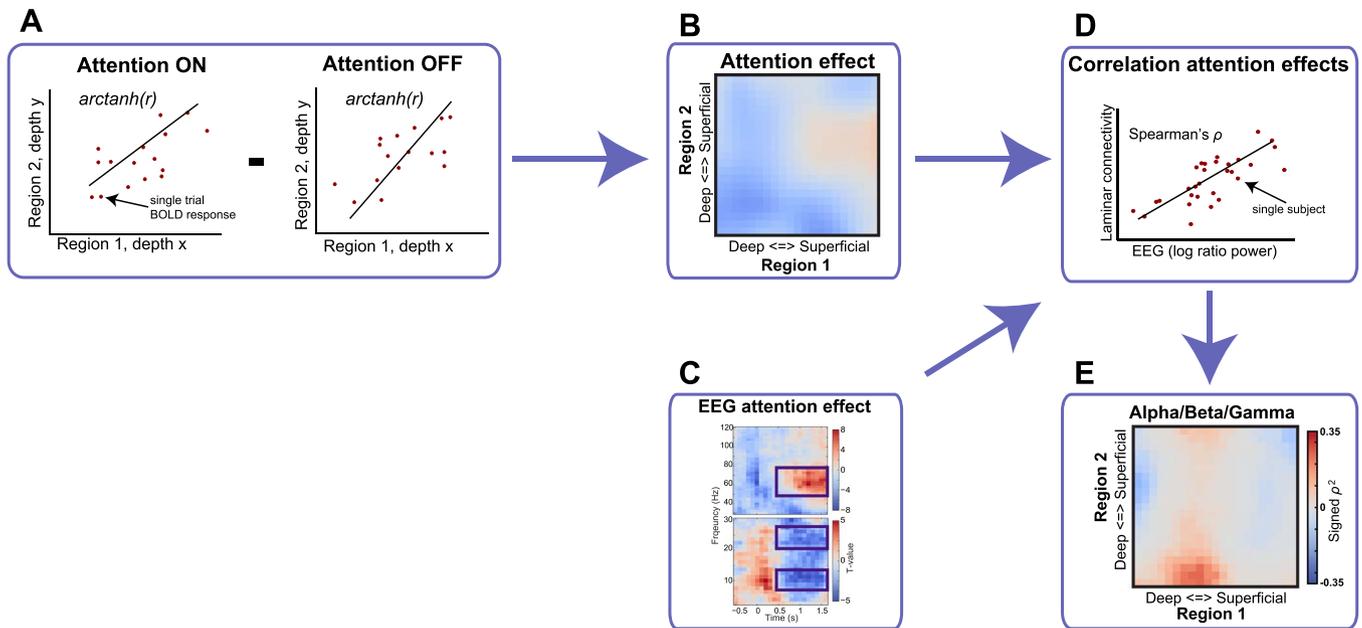


Fig. 2. Schematic representation of the analysis pipeline. Single-subject laminar connectivity was computed for each single depth-by-depth combination as the Fisher's z -transformation of the Pearson correlation (r) between the amplitude of single-trial BOLD responses (A) for both conditions and separately for each block. Single-trial amplitudes were obtained through fitting a canonical hemodynamic response function for every trial using a regression approach. The attention effect for a single subject, depicted for each depth combination between regions in B, is computed as the difference between these z -transformed correlations averaged over the 3 experimental blocks. The single-subject attention effects in the alpha, beta, and gamma bands (C) were correlated over subjects with the single-subject attention effects in laminar connectivity (D) using Spearman's rank-order correlation (ρ). After squaring and multiplication with the sign of the correlation, the laminar level relation of EEG frequency band with depth-resolved connectivity between region pairs can be assessed separately for alpha, beta, and gamma (E). For the analysis presented in the main article, laminar connectivity was first averaged over the region pairs indicated in Fig. 3 before the attention effect was calculated.

monotonic, but not linear relationship) was calculated between the attention effects in laminar connectivity and the EEG frequency bands and pupil size. For each frequency in question, the effects in the other 2 frequency bands and pupil size were controlled for. For pupil size, the correlation was controlled for the 3 EEG frequency bands. Significance was determined by a nonparametric cluster-based test (Maris and Oostenveld 2007) applied to correlations that is described in full detail in our previous work (Scheeringa et al. 2016). A cut-off of $P < 0.05$ uncorrected (2-sided) was used to determine the clusters and 200,000 permutations were used to calculate the reference distribution of cluster-sums.

A schematic representation of how we computed laminar connectivity and its relation to EEG power is depicted in Fig. 2. In Fig. 2A, we illustrate how we compute the attention effect in laminar connectivity for a single inter-/intraregional combination of laminar depths, which was repeated for all region/depth combinations. We computed the attention effect in laminar connectivity in the following steps: First, we estimated the amplitude of single-trial BOLD responses for the 2 conditions without a speed increase (attention ON and attention OFF) by fitting a canonical hemodynamic response function. Subsequently, for each condition separately, the correlation of these amplitudes over trials was calculated (excluding erroneous trials and trials with eye blinks). After applying a Fisher z -transformation (i.e. $\text{arctanh}(r)$) to account for ceiling effects, these were averaged over

the separate task blocks and grouped into interregional connectivity within a hemisphere and intraregional connectivity within the brain regions (see Fig. 3A and E). Subsequently, for each of the groups the attention contrast was calculated by subtracting the connectivity metric for the "attention OFF" condition from the "attention ON" condition, the result of this analysis is illustrated in Fig. 3B. In order to relate EEG frequency bands to laminar fMRI connectivity, this attention contrast was then correlated over subjects (Fig. 3D) separately with the attention effects in, respectively, the alpha, beta, and gamma bands (Fig. 3C) using a partial Spearman correlation (correcting for effects in the other frequency bands and in pupil size; Supplementary Fig. S1). This results in a 2-dimensional representation of how laminar fMRI connectivity relates to a specific EEG frequency band, illustrated in Fig. 3E. The results of these analyses are depicted in Fig. 3B–D and F–H.

Results

Previous results

A full account of our previous results can be found in Scheeringa et al. 2016. In Fig. 1, we present the results from this work that are relevant for the analyses carried out here. In Fig. 1B–D, we depict the relevant results from this attention contrast taken from our previous work. In Fig. 1B, we show a time–frequency representation of the effects on EEG power. It shows that alpha and beta

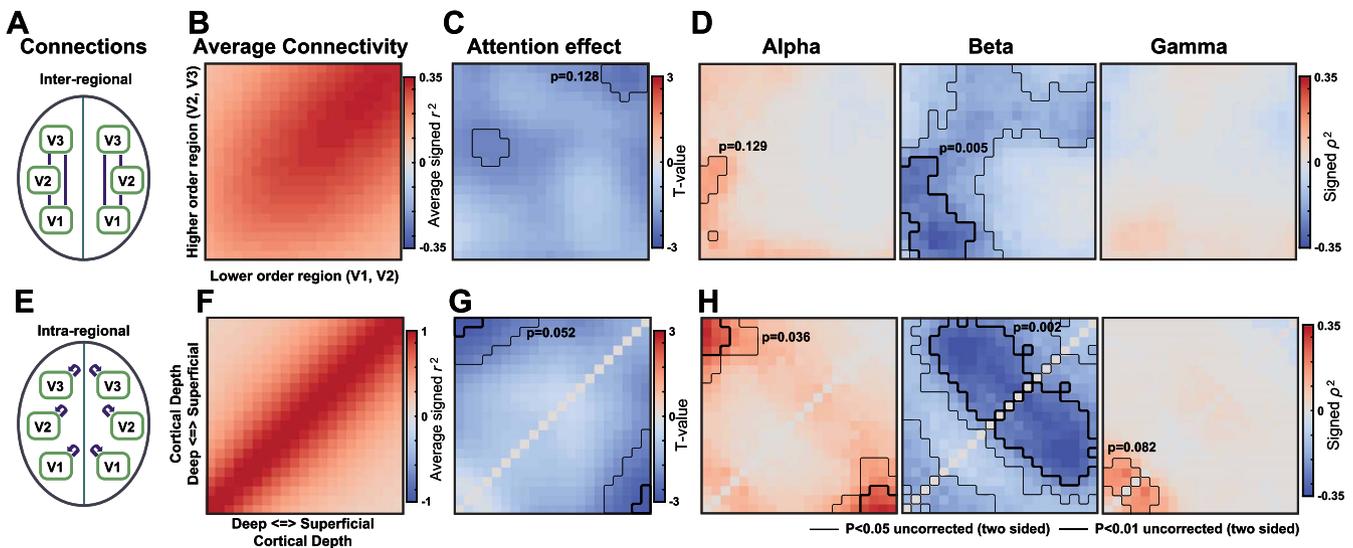


Fig. 3. Relation between EEG power and inter-regional and intra-regional laminar fMRI connectivity. The top row (A–D) depicts the results for inter-regional connectivity. The bottom row (E–H) depicts the results for intra-regional connectivity. The left column (A and E) illustrates for each row the connections over which connectivity was averaged, and the results in the panels to the right apply. For inter-regional connectivity depicted in the top row, the lower order region in the visual hierarchy is plotted on the x-axis and the higher order region on the y-axis. For all panels, except A and E, deep-to-superficial cortical depths are depicted from left to right on the x-axis, while on the y-axis they are depicted from bottom to top. Panels (B) and (F) depict the average connectivity over attention ON and attention OFF conditions, calculated as the average over runs conditions and subjects of the squared Pearson correlation multiplied by the sign of the correlation. Panels (C) and (G) show the attention task effect on laminar connectivity expressed in t-values, based on individual attention effects that were calculated as the difference between attention ON and attention OFF conditions. Panels (D) and (H) show the relation between attention effect in EEG power for the indicated frequency bands and laminar fMRI connectivity. The signed squared partial Spearman correlation over subject ($n = 30$) is shown. For each frequency band, the effects of other frequency bands and pupil size are partialled out. Since connectivity within regions is depicted in F–H, the results are symmetric about the $x = y$ diagonal. P-values relate to the largest suprathreshold cluster in each sub-panel that contributed to the nonparametric cluster-based permutation test. The $P < 0.05$ uncorrected threshold was used as the cluster level threshold. The relation between pupil size and inter-regional connectivity is depicted in [Supplementary Fig. S1](#). The results for inter-regional connectivity based on the top 5% and top 25% activated vertices are shown in [Supplementary Figs. S2](#) and [S3](#). The results for the individual region combinations underlying the averages presented here are depicted in [Supplementary Figs. S4](#) and [S5](#).

power in the last second of the trials are lower during “attention ON” trials than during “attention OFF” trials, while gamma power is higher during the “attention ON” condition. In [Fig. 1C](#), we show stronger BOLD activation during the ON condition across all cortical depths in V1, V2, and V3. The analyses presented here were carried out on BOLD data averaged from the top 10% activated pairs of vertices in each region (changing the 10% threshold value to 5% and 25% did not yield a qualitatively different picture). The results for [Fig. 1C](#) show that attention modulation leads to an increased BOLD response across all cortical depths in all 3 regions. In [Fig. 1D](#), we show the (signed squared) partial correlation between the attention effects in EEG power and those in laminar BOLD, while controlling for the effect of pupil diameter. These analyses show that the EEG alpha attention effect is negatively correlated with the BOLD attention effect in superficial layers for all regions, while the beta effect correlates negatively with the deep layer BOLD attention effect. For gamma, we observed a positive correlation in middle/superficial depths for V2 and V3 and across all cortical depths for V1.

New results

Our main results are presented in [Fig. 3](#) where the first column shows which connections are being considered to obtain the results in the corresponding row. The top row depicts the results for inter-regional connectivity

within a hemisphere and the bottom row depicts the results for intra-regional connectivity. In the original analysis of these data, we observed an attention effect in pupil size, which is depicted in [Supplementary Fig. S1](#), where we also show the correlation of the pupil-attention effect with laminar connectivity within and between regions, observing no significant effects. The results presented here are based on the top 10% activated vertex pairs. The results for the top 5% and top 25% activated vertex pairs are depicted in [Supplementary Figs. S2](#) and [S3](#). The results for individual region interactions, averaged over homologue connections in both hemispheres, are depicted in [Supplementary Figs. S4](#) and [S5](#).

[Figure 3B](#) depicts the average fMRI connectivity summed over the 2 conditions for inter-regional connectivity while [Fig. 3F](#) shows the same for intra-regional connectivity. Inter-region connectivity increased along the diagonal from deep-to-deep connectivity pairings to superficial-to-superficial pairings, in accordance with previous observations ([Wu et al. 2018](#)). Due to partial volume effects, connectivity is strongest close to the diagonal for intra-regional connections (on the diagonal it is 1 by definition). In [Fig. 3C](#) and [G](#), we depict the attention effects in BOLD connectivity. Between regions ([Fig. 3C](#)), no strong laminar-specific effects were observed, although there is a global trend that indicates a relative decrease in connectivity with attention compared to without attention. Within brain regions

(Fig. 3G), a relatively strong, negative effect was found for connectivity between deep and superficial layers, as well as a nonspecific decrease with attention similar to the one observed in for interregional connectivity.

In Fig. 3D and H, we show how the attention contrast in laminar connectivity correlates with the attention effect in EEG power. The most prominent observation is that decreased beta band power strongly relates (over subjects) to increased laminar-specific connectivity inter-regionally as well as intra-regionally. For inter-regional laminar interactions, beta power correlates “negatively” with deep-to-deep layer connectivity, while for intraregional connectivity it correlates to deep-/middle to middle/superficial connectivity. For the alpha band, we observe a “positive” correlation with intraregional deep-to-superficial layer connectivity. Although there is no strong effect observed for alpha for interregional connectivity, the same positive trend as for intraregional connectivity seems to be there. The relationship of EEG alpha power with deep-to-superficial intraregional connectivity shows a similar pattern to the attentional decrease in fMRI connectivity (compare Fig. 3G and H). The effects described here are further illustrated in Fig. 4 by the scatter plots depicting the underlying correlation for the strongest cortical depth combinations inside the clusters that lead to our significant observations.

To verify whether the effects observed for the alpha and beta bands are stable over analysis strategies, we repeated the analysis for the laminar signals extracted from the top 5% (Supplementary Fig. S2) and top 25% (Supplementary Fig. S3) activated signals. These analyses (particularly for the top 5%) yielded qualitatively similar results to those presented above. Where we find clusters of a strong relationship in the main analysis here, we find effects of the same nature, except for possibly for the relationship of beta with intra-regional connectivity for the top 25% activated voxels where the relationship is weak, but similar to that of the top 5%. Similarly, the results for the single region pairs suggest that inter- and intra-regional connectivity are also largely consistent with the average over individual region combinations (see Supplementary Figs. S4 and S5), although some differences can be observed in for instance a substantially weaker relationship of beta with intra-regional connectivity within V1 and a negative correlation of beta with superficial layer V2 to deep layer V3 connectivity.

Discussion

In this study, we explore how task-related changes in fMRI connectivity within and between brain regions relate to changes in neural synchronization measured by frequency-specific EEG power. We used an attention-demanding visual change detection task, which allowed us to correlate task-induced differences in alpha, beta, and gamma power to depth-dependent connectivity between regions and within regions. We observed the

strongest link between laminar fMRI connectivity and EEG power for the beta band. The negative correlation between beta power and deep-to-deep interregional layer connectivity as well as deep/middle to superficial layer connectivity indicates that a decrease in beta power reflects an increase in laminar specific connectivity. For the alpha band, we observed a positive correlation pattern for intraregional connectivity, which strongly resembles the inverse of the pattern of decreased fMRI connectivity as a result of the attentional modulation. For both the attentional modulation and the correlation with alpha power, a strong effect was observed for the deep-to-superficial intraregional layer connection. For interregional connectivity, no significant relation with the alpha band was observed, although in general, a positive relation was present as well. This indicates that, in contrast to beta band decrease, the task-induced alpha band decrease relates to decreased laminar connectivity, particularly within a region. For the gamma band, no relation was observed with laminar connectivity within regions, indicating that while gamma band activity is related to the strength of the BOLD signal in middle and superficial layers, this is not reflected in changes in laminar fMRI connectivity within and between brain regions. The general patterns observed for the aggregated inter- and intra-regional coupling were also reflected in the individual region pairs (inter-regional) and regions (intra-regional), although unique features were also observed, suggesting that the aggregate results reflect a more general pattern.

The results for the beta band presented here support a notion that especially deep-to-deep layer feedback projections are related to beta band activity (Buffalo et al. 2011; Bastos et al. 2012; Bastos et al. 2015). This is further supported by our previous finding from this dataset that beta power correlates negatively with BOLD activity in deep layers (Scheeringa et al. 2016), which aligns well with observations in EEG and MEG that beta power, like alpha power, often decreases in regions that become actively involved in a task (Spitzer and Haegens 2017). On the other hand, inter-areal beta-band synchrony is regularly reported to increase when brain regions become task involved (Buschman and Miller 2007; Bastos et al. 2015; Schoffelen et al. 2017). This leads to a pattern of locally decreased beta band activity, reflected in a power decrease in EEG and MEG, and greater inter-regional beta band synchronization, which is typically better measured intracranially in animals. Here we find the deep-layer inter-regional connectivity increases for subjects that show a stronger task-related beta power decrease. Following from the pattern described above, this increase might reflect the same underlying process that is reflected in (deep-to-deep layer) interregional beta band synchrony observed in animals. In addition, within a brain region, we observed that a decrease in beta power predicts increased connectivity between deep/middle and superficial layers. Combined with the observation that beta correlates negatively with deep layer BOLD,

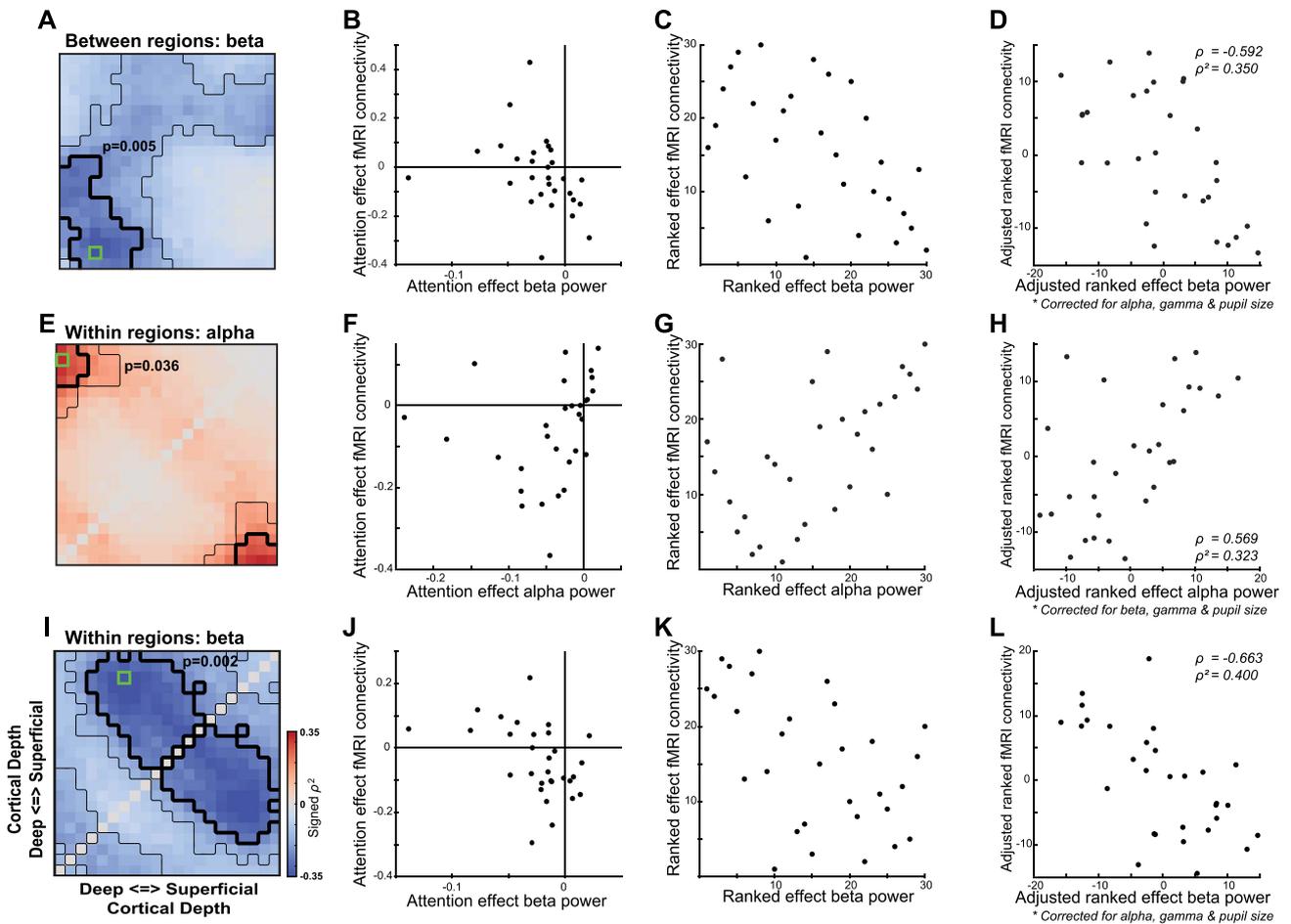


Fig. 4. Scatter plots for depth combinations where the attention effect in fMRI connectivity shows the strongest relationship with the attention effect in EEG. In A, E, and I, we show, respectively, the relationship with inter-regional connectivity with beta power, intra-regional connectivity with alpha power, and intra-regional connectivity with beta power as presented in Fig. 3. In green, we indicate the data point with the strongest relationship. The scatter plots to the right relate to this data point. In panels B, F, and J, we depict for these points the underlying attention effect in EEG power and laminar connectivity of each subject in a scatter plot. The attention effect for fMRI connectivity was calculated as the difference in Fisher Z-transformed Pearson correlation for the 2 attention conditions. The attention effects for EEG as the log of the ratio between power in the attention ON and attention OFF conditions. To account for the influence of outliers, as is apparent in some of these plots, we calculate the (squared) partial Spearman correlation. The third column (C, G & K) shows the rank ordered version of the data in column 2 (B, F, and J). The fourth column (D, H, and L) is computed from the third column by removing the rank ordered attention effects in the other 2 frequency bands and in pupil size through linear regression. The partial Spearman correlation can then be computed as the (normal) Pearson correlation between the 2 variables depicted here.

and deep-to-deep layer interregional connectivity, these findings suggest that within a brain region a decrease in beta power reflects increased incoming feedback-related information in deep layers that is subsequently projected to middle/superficial layers.

For the alpha band, our main finding is that decreased alpha power (in the attention ON compared to the attention OFF condition) relates strongly to decreased correlations between deep and superficial layer BOLD responses within the same region. This is in line with the observation in laminar recordings in monkeys that connected alpha sources can be found in both infragranular and supragranular layers (Bollimunta et al. 2008; Bollimunta et al. 2011; Haegens et al. 2015). Typically, alpha is seen as either an idling rhythm that occurs when the cortex is not task involved, or a reflection of top-down inhibition of task irrelevant brain regions (Pfurtscheller et al. 1996a; Klimesch et al. 2007; Jensen and Mazaheri 2010). The results here suggest that these processes might be

reflected in greater correlations between deep and superficial layer activity within regions. The inhibition or idling function of an increased alpha amplitude seems to be reflected in lower, but more correlated, neural activity across layers. This increased correlation might reflect a lower capacity for independent and differentiated neural responses in different layers of the cortex. Task-evoked decreases in inter-neural coupling have been previously observed in spike rate correlations and fMRI connectivity (Cohen and Maunsell 2009; Ecker et al. 2010; Cole et al. 2014; Ruff and Cohen 2014; Gonzalez-Castillo and Bandettini 2018; Ito et al. 2020). Our results here suggest that these decreases relate to task-evoked changes in local neural synchronization in the alpha band.

A noteworthy observation here is the lack of a relation between gamma band activity and laminar connectivity. Gamma band activity is thought to reflect feedforward flow of information from lower order superficial to higher order middle cortical layers (Bastos et al. 2012;

Bosman et al. 2012; Bastos et al. 2015; Fries 2015), which is reflected in increased coupling between (laminar resolved) electrophysiological measures from different regions (Bosman et al. 2012; Grothe et al. 2012; Roberts et al. 2013; van Kerkoerle et al. 2014; Michalareas et al. 2016). In line with this, we found gamma band activity to correlate positively with middle/superficial layer BOLD responses to visual stimulation (Scheeringa et al. 2016). We however did not find this reflected in a relation between gamma and laminar connectivity. Our results therefore suggest that neural and cognitive processes related to laminar-specific interactions with increased gamma-band synchrony might not be well studied by approaches based on fMRI-based laminar-level coupling.

Our observation that alpha and beta band activity have relationships with fMRI laminar connectivity that differ in sign (especially within a brain region) is surprising, since both bands show an attentional decrease in power and negatively correlate with the BOLD signal (Fig. 1D). Since alpha is thought to indicate functional inhibition or idling of task irrelevant regions (Pfurtscheller et al. 1996a; Klimesch et al. 2007; Jensen and Mazaheri 2010), our results suggest that increased BOLD connectivity, most pronounced for connectivity between layers within a region, can be a sign of decreased task involvement of connected but separate neural populations. Likewise, beta power is often observed to decrease in a context where regions become involved in task execution and increase when involvement stops, as is illustrated by the motor-related beta-rebound (Salmelin et al. 1995; Pfurtscheller et al. 1996b). However, for beta, a negative correlation with laminar connectivity between and within regions is observed. Combined, these results for the alpha and beta bands indicate that an increase as well as a decrease in (laminar) fMRI connectivity measures can indicate greater involvement in the same task of separate neural populations (e.g. in different layers or regions). In general, this observation complicates the interpretation of fMRI-based laminar and nonlaminar connectivity in isolation.

We observed the strongest correspondence between the pattern across cortical depth combinations for the attention effect in laminar connectivity and the pattern observed for correlation with alpha band EEG power (Fig. 3G and H). The positive correlation for alpha power with deep-to-superficial layer connectivity resembles the attention modulation-related decrease in connectivity. Since attention induces a decrease in alpha power, this indicates that subjects with a stronger attention-related alpha decrease have a stronger decrease in deep-to-superficial intra-regional connectivity. For beta, the correlation with laminar connectivity is negative for both inter- and intra-regional laminar connectivity (Fig. 3D and H). Since beta power also decreases with attention, this suggests that stronger attention-related decreases in beta power result in higher laminar level connectivity within and between regions. This is however not reflected in the attention effect observed for laminar

connectivity (Fig. 3C and G), which tend to show a more general negative effect (although not significant). These results in our view indicate that observed task effects in (laminar) fMRI connectivity can be simultaneously affected by processes that increase and decrease intra- and inter-regional connectivity. Being able to relate (laminar) fMRI connectivity effects to EEG measures can contribute to disentangling these effects as is demonstrated here. However, a comparison of the pattern of attention effects in connectivity between regions in panels C and G of Fig. 3 with the observed relation with EEG frequency band in panels D and H suggests that the pattern in attention effects cannot fully be explained by the EEG frequency bands investigated here. It is improbable that the patterns of correlations observed for the correlation with EEG reflect all the neural effects that contribute to the pattern of attentional effects in laminar connectivity. This observation implies that there are influences on task-related fMRI connectivity changes that are not reflected in EEG power. It is important to note that fMRI does not measure neural activity in the same way as EEG and MEG. The latter critically depends on phase-synchronous responses in post-synaptic membrane potential of a part of the underlying neural population (apical dendrites of pyramidal cells), while fMRI can better be considered a representation of, temporally low-pass filtered, total synaptic activity of the measured population.

Combined with the observation that task effects in alpha correlated with task effects in superficial layer BOLD and beta with task effects in deep layer BOLD, the laminar fMRI results indicate distinct neural mechanisms underlying the alpha and beta effects and therefore likely relate to distinct cognitive processes. In experiments that test the predictive coding framework, and also in animal electrophysiological work in general, these frequency bands are often not assessed separately (Buffalo et al. 2011; Bauer et al. 2014; Bastos et al. 2020). The finding that stronger alpha oscillations relate to stronger coupling between neural populations might reflect a less differentiated neural response to stimuli. Within a predictive coding framework, this increased coupling might be interpreted with decreased precision (of the prediction) when alpha amplitude increases, while the predictions themselves are related to beta band oscillations.

EEG power is believed to be a reflection of synchrony between neurons in post-synaptic potentials within a specific frequency band over a larger part of the cortex (Lopes da Silva 2013). Considering the limited spatial resolution of EEG and previous observations that this task and similar tasks induce power changes across several regions in early visual cortex, the attention-related power changes we consider here therefore likely reflect the sum of synchronous post-synaptic potentials in regions in early visual cortex. Since EEG power is thought to reflect synchronous post-synaptic activity, stronger coupling in activity between neurons (within the same or in

different regions) could be expected when synchrony (e.g. EEG power) is higher regardless of the frequency band. Therefore, a positive correlation could be expected for all 3 frequency bands investigated here. We do not find this. Only for alpha power, do we find stronger coupling between layers within regions. For beta power, we find the opposite effect both within and between regions, while for gamma power no relation was observed for either. There are several factors that could be related to this. The neural synchrony we measure with EEG is related to millisecond level synchronization of post-synaptic potentials of only a subpopulation of neurons (parallel oriented pyramidal cells). The fMRI BOLD signal is more related to the total amount of peri-synaptic activity as far as it results in a local change in blood flow, and therefore does not depend on the millisecond level synchrony necessary for detectable oscillations in EEG, and is also the direct consequence of neural activity in a larger neural population. The relation between frequency-specific EEG synchrony and laminar connectivity therefore is also likely a relation between at least in part different types of neural activity.

The ability to study fMRI connectivity at the laminar level is a relatively recent development. Besides linking laminar fMRI connectivity to frequency-specific EEG power, the findings here also provide insight to laminar fMRI itself. A first pattern that emerges from our analysis is that irrespective of attention condition, we observed that connectivity increased along the diagonal from deep-to-deep connectivity pairings to superficial-to-superficial pairings. This is in line with earlier observations of connectivity between voxels within a region (Wu et al. 2018) and is likely related to the larger contribution to the BOLD signal from draining veins which increases towards the surface of the cortex. When we subsequently compare the attention ON versus the attention OFF condition, the outcomes do suggest a general decrease in fMRI connectivity with attention for both within and between region connectivity, although no significant results were observed for our crude attention modulation in laminar fMRI connectivity within and between regions. While no particular laminar pattern stands out for connectivity between regions, for within region connectivity, a pattern of decreased coupling between deep and superficial layers stood out that resembles the positive correlation observed with alpha power (Fig. 4C and D). Since our task manipulation is not a clean modulation of attention but also includes cognitive processes like arousal and the predictability of the speed change, these decreases in connectivity cannot directly be linked to a specific cognitive process. It is however not uncommon to observe task-evoked decreases in neural correlations within a region and between connected cortical regions in both neural spiking and fMRI connectivity (Cohen and Maunsell 2009; Cole et al. 2014; Ruff and Cohen 2014; Gonzalez-Castillo and Bandettini 2018; Ito et al. 2020). Since our experimental manipulation essentially consisted of a task ON versus task OFF contrast, our

results might reflect the same or a similar process. Our results suggest that this process of decorrelation of neural populations, especially between different layers in the same region, is related to a decrease in alpha power.

The analyses in this study are based on 30 subjects, making it one of the larger studies using laminar fMRI to date. It is however still on the small side compared to other studies relating individual differences in (f)MRI-based measures to other measures over subjects. In addition, while some studies have previously linked EEG to fMRI connectivity (Scheeringa et al. 2012; Lenartowicz et al. 2016), linking EEG to cortical depth-resolved fMRI connectivity is still unexplored territory. Furthermore, the results presented here come from a post hoc exploratory analysis on an existing data set. Therefore, we see this study as a proof of principle that demonstrates that changes in fMRI-based laminar connectivity relate to changes in the strength of EEG connectivity. The exact pattern and nature will no doubt be subject of further research.

In conclusion, this exploratory study provides the first evidence that neural oscillations measured by EEG reflect not only laminar-specific neural activity but also changes in laminar-specific connectivity within and between brain regions. As such, it provides a neurophysiological basis for investigating laminar level connectivity with fMRI. It further suggests that the neural processes underlying alpha and beta oscillations are associated with opposite effects in correlation-based connectivity measures in (laminar) fMRI, while their relations to the strength of the BOLD response and modulation by task conditions are highly similar. If this observation is indeed further verified, this could have important implications for correlation-based measures of functional and effective connectivity. This would imply that it is crucial to understand in which conditions alpha and beta neural oscillations are modulated in order to understand the effects of (laminar) connectivity changes in fMRI. Integrated analysis of laminar fMRI connectivity with electrophysiological measures like EEG and MEG might provide further insights on this topic.

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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