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Linking cortical circuit models to human cognition with laminar fMRI

Jiajia Yang^{a,b,*}, Laurentius Huber^c, Yinghua Yu^{a,b}, Peter A. Bandettini^{b,d}

^a Graduate School of Interdisciplinary Science and Engineering in Health Systems, Okayama University, Okayama, Japan

^b Section on Functional Imaging Methods, National Institute of Mental Health, Bethesda, MD, USA

^c MR-Methods Group, Faculty of Psychology and Neuroscience, University of Maastricht, Maastricht, the Netherlands

^d Functional MRI Core Facility, National Institute of Mental Health, Bethesda, MD, USA

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ABSTRACT

Laboratory animal research has provided significant knowledge into the function of cortical circuits at the laminar level, which has yet to be fully leveraged towards insights about human brain function on a similar spatiotemporal scale. The use of functional magnetic resonance imaging (fMRI) in conjunction with neural models provides new opportunities to gain important insights from current knowledge. During the last five years, human studies have demonstrated the value of high-resolution fMRI to study laminar-specific activity in the human brain. This is mostly performed at ultra-high-field strengths (\geq 7 T) and is known as laminar fMRI. Advancements in laminar fMRI are beginning to open new possibilities for studying questions in basic cognitive neuroscience. In this paper, we first review recent methodological advances in laminar fMRI and describe recent human laminar fMRI studies. Then, we discuss how the use of laminar fMRI can help bridge the gap between cortical circuit models and human cognition.

1. Why is the understanding of cortical layers important?

The human cerebral cortex contains billions of neurons that are organized into well-defined laminar structures, and the neurons in each layer have thousands of interlaminar and cortico-cortical synaptic connections with other neurons. Currently, knowledge of the laminarspecific function of the cerebral cortex is heavily reliant on findings obtained from laboratory animal models using invasive methods (Barbas, 2015; Goulas et al., 2018), and there is still a gap between the findings from laboratory animals and humans. Thus, the mapping of laminar-specific activity in the human brain is an exciting approach that promises to provide insight into the function of the human brain. For example, much of visual neuroscience has been built on the notion of a visual cortical hierarchy (Felleman and Van Essen, 1991; Hilgetag et al., 2000; Zeki and Shipp, 1988). Crucially, this hierarchical arrangement is based upon the distinction between feedforward and feedback connections¹. In turn, the difference between a feedforward and feedback connection is defined almost exclusively in terms of laminar-specific connections. This simple fact emphasizes why being able to measure laminar-specific responses is important for characterizing hierarchical functional architectures in the human brain (Haeusler and Maass, 2007; Lawrence et al., 2017; Self et al., 2019). Furthermore, understanding cortical layers will open a new window in elucidating the basis of severe mental disorders (e.g., autism and schizophrenia) and neurodegenerative diseases (e.g., Parkinson's disease and Alzheimer's disease), as these disorders are accompanied by specific impairments in laminar-specific circuitry in the brain (Arnsten et al., 2019; Lewis, 2012; Liu et al., 2020; Munoz et al., 2017).

Recently devised *in vivo* ultra-high-field (UHF), high-resolution (submillimeter-level) functional magnetic resonance imaging (fMRI) has begun to directly reveal laminar-specific brain activity in the human brain. This noninvasive imaging method, known as laminar fMRI² (Huber et al., 2015, 2017, 2019, 2020; Kashyap et al., 2018; Nasr et al., 2016; Norris and Polimeni, 2019; Olman et al., 2012; Polimeni and Uludağ, 2018; Puckett et al., 2016), bridges the gap between findings from laboratory animals and humans. Fig. 1 illustrates the conceptual

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^{*} Corresponding author at: Applied Brain Science Lab, Graduate School of Interdisciplinary Science and Engineering in Health Systems, Okayama University, 3-1-1 Tsushima-Naka, Kita-ku, Okayama, 700-8530, Japan.

E-mail address: yang@okayama-u.ac.jp (J. Yang).

¹ The terms feedforward and feedback are historical terms that can be considered largely anatomical. Current accounts of laminar-specific connectivity refer to forward and backward connections. This is because the feedback in predictive processing is conveyed by the forward connections in the form of prediction errors. ² We use the term "laminar fMRI" throughout this article to refer to fMRI at spatial resolutions that are capable of resolving depth-dependent activity, but we are not necessarily referring to individual cortical layers as defined cytoarchitectonically.

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framework of this article. In this article, we begin by reviewing the nature of multiscale (i.e., spatial scale) brain function and how it will benefit us in understanding brain function at the laminar level. Then, we review the recent methodological advances in laminar fMRI and highlight the state-of-the-art studies that have successfully used laminar fMRI to address basic questions. We then summarize what these studies reveal about cortical circuit models. Furthermore, we discuss how the use of laminar fMRI can help link cortical circuit models to human cognition. Finally, we highlight potential future research directions and describe the limitations of laminar fMRI. We envision that this review will prompt more researchers to focus on improving the laminar fMRI methodology and to apply this method in the understanding of human cognition from a laminar neuroimaging perspective.

2. Approaching brain function across multiple spatial scales

The use of laboratory animals in research has provided valuable insights into understanding human cognition at multiple scales. As shown in Fig. 2A-D, using various approaches and comparative analyses across species at different spatial scales has provided well-defined cortical circuit models that are suitable for translating brain function findings across species.

At the behavioral level, the comparison of cognitive and behavioral capacities between humans and nonhuman primates (NHPs) helped us to understand how functional activity underlying those tasks has evolved in humans. For example, the patterns of behavioral performance for visual object recognition in rhesus monkeys are highly correlated with those in humans (Fig. 2A), which may suggest that a common neural shape representation in the brain is shared across species (Rajalingham et al., 2015). The establishment of the use of the blood oxygenation level-dependent (BOLD) contrast-based fMRI technique (Bandettini, 2012; Bandettini et al., 1992; Kwong et al., 1992; Ogawa et al., 1992) in the early 1990s revolutionized the study of human brain functions. The advances in whole-brain coverage with 2-mm isotropic resolution at 3 T fMRI have enabled researchers to identify hitherto unobserved forms of human brain activity and structural/functional connectivity related to human cognition (Christophel et al., 2017; Glasser et al., 2013; Uğurbil et al., 2013), and it also enabled direct comparison of brain function between humans and NHPs (Kriegeskorte, 2009; Kriegeskorte et al., 2008). For example, at the whole-brain level, a previous fMRI study found very similar resting-state functional connectivity patterns in both humans and macaques (Fig. 2B) (Neubert et al., 2014). To date, fMRI with millimeter-level spatial resolution can be routinely used, and significant progress has been made in understanding the brain network basis of cognitive functions by comparing

NHP and human brains.

To allow interspecies comparisons at the cortical laminar/columnar level, researchers are putting more effort into developing high-field fMRI methodology to robustly image at the submillimeter level (Norris and Polimeni, 2019; Olman et al., 2012; Polimeni and Uludağ, 2018; Yacoub and Wald, 2018). In the early days, several landmark studies used a 4 T MRI scanner to observe human ocular dominance columns (Cheng et al., 2001; Menon et al., 1997). Because of the success of the generation of 7 T MRI systems, a human fMRI study demonstrated the existence and spatial features of orientation selective columns in the human primary visual cortex (V1) (upper panel, Fig. 2C) (Yacoub et al., 2008). Such functional columnar organization could previously be detected only in NHP brains (e.g., lower panel, Fig. 2C) (Bonhoeffer and Grinvald, 1991; Hubel and Wiesel, 1974; Okamoto et al., 2011). Despite the improvements that these advances in neuroimaging technology offer, the direct comparison of the functional organization across species remains challenging (Fig. 2D). Currently, UHF fMRI at 7 T is developing into a mature technology that has already had a major impact on neuroimaging as it moves laminar fMRI closer to becoming a platform for linking cortical circuit models to human cognition.

3. Technological advances in laminar fMRI

The main advantage of the UHF MRI system is the stronger magnetic field, resulting in an increased signal-to-noise ratio (SNR) (Nowogrodzki, 2018), which can be translated into higher spatial resolution. For example, the sensitivity of 7T but not yet 3T fMRI at 0.7mm (in-plane) is sufficient to capture finger tapping-evoked brain activity in the primary motor cortex (M1) (Fig. 3A). By increasing the spatial resolution from 2.0 mm to 0.7 mm at 7 T, the expected laminar-specific double stripe pattern (Fig. 3B) was identified (Huber et al., 2018b). Furthermore, the selection of appropriate image contrast is critical for laminar fMRI. For example, compared to conventional gradient-echo (GE) BOLD contrast, cerebral blood volume (CBV) contrast is more sensitive in observing the distribution pattern of laminar activity in specific areas (Fig. 3C). Currently, the superior sensitivity of GE-BOLD contrast makes it the most widely applied method for laminar fMRI (Dumoulin et al., 2018). However, GE-BOLD contrast is more sensitive to signals from large blood vessels, with the result that the GE-BOLD signal is biased towards the ascending veins and the large veins on the pial surface (Dumoulin et al., 2018; Huber et al., 2019) (Fig. 4A). This disadvantage results in a general signal increase towards superficial layers, which obscures the underlying laminar profiles. Since the ascending veins are located in the cortex every 200-500 µm, masking them in high-resolution BOLD cannot fully account for spatial signal



Fig. 1. Schematic approach for linking cortical circuit models to human cognition using laminar fMRI. Laminar fMRI allows us to acquire laminar-specific activation data in the human brain. Combining laminar fMRI with invasive neurophysiological measures in nonhuman primates will help researchers establish a modeling-validation loop to identify potential relationships between neural activity and the fMRI signal. Moreover, the higher spatial resolution of laminar fMRI enhances our capacity to resolve directional connectivity in brain networks by adding the third dimension (i.e., cortical depth) of the cortex.

Neuroscience and Biobehavioral Reviews 128 (2021) 467-478



Fig. 2. Multiscale comparison between human and nonhuman primates (NHPs), from behavior to whole-brain function and microcircuits to neurons. (A) Confusion matrices of humans and rhesus monkeys performing the same visual object recognition task (Rajalingham et al., 2015). (**B**) Whole brain resting-state connectivity patterns of the human and macaque inferior frontal sulcus (IFS) (Neubert et al., 2014). (**C**) Visual orientation columnar patterns in the human primary visual cortex (V1), obtained via an ultra-high-field (UHF) fMRI study at 7 T (Yacoub et al., 2008), and in macaque V1 (Okamoto et al., 2011), obtained by optical imaging. (**D**) Existing understanding of the laminar-specific structure/functions of the cerebral cortex is heavily reliant on electrophysiological measures in NHPs (van Kerkoerle et al., 2017). Currently, laminar fMRI facilitates direct comparisons of human laminar-specific brain function to the findings from previous NHP studies.

leakage. One approach to tackle this problem is the use of spin-echo (SE) BOLD contrast. For instance, some recent studies (Han et al., 2019; Norris, 2012; Olman et al., 2012; Vu et al., 2018) indicated that SE-based BOLD contrasts have higher specificity for the microvasculature, and the large vein signals are significantly reduced compared to GE-BOLD contrast. Even at UHF, however, SE-BOLD sequences suffer from some contamination of intravascular (large vessel) signals, thus confounded by intracortical ascending veins from the deeper to the superficial layers, which will also bias the signals across layers. To account for these disadvantages of BOLD contrasts, cortical depth-dependent hemodynamic models (Heinzle et al., 2016) and vasculature distribution models (Havlicek and Uludag, 2020; Markuerkiaga et al., 2016; Marquardt et al., 2018) are becoming more prevalent.

One alternative approach to minimize the draining vein effect of BOLD contrasts is the use of non-BOLD contrasts to obtain CBV maps of cortical activity. To date, we think the most used sequences for non-BOLD contrast laminar fMRI in humans are slice-saturation slab-inversion vascular space occupancy (VASO) for CBV mapping (Huber et al., 2019). This contrast appears to be much more selective for hemodynamic changes at the very small vessel and capillary level within specific layers (Fig. 4B). For an empirical data example (Fig. 4C), the activation-induced GE-BOLD signal peaks at or above the cortical surface, whereas the CBV signal peaks slightly deeper and within gray matter in human M1 (Huber et al., 2015). However, the CBV contrast suffers from reduced sensitivity relative to BOLD as well as low time efficiency, as it needs some degree of extra time for functional contrast preparation pulses. In summary, conventional BOLD contrasts are widely used in the field of laminar fMRI (Kok et al., 2016; Lawrence et al., 2018; Muckli et al., 2015), whereas laminar fMRI with non-BOLD contrasts is just beginning to be used in human studies (Finn et al., 2019; Huber et al., 2017; Persichetti et al., 2020; Yu et al., 2019). Each contrast has its advantages and disadvantages (Fig. 4D) depending on the MRI

scanner environment and their research questions (for details, see review (Huber et al., 2019).

Regardless of these features of each contrast, it remains challenging for laminar fMRI with both BOLD and non-BOLD contrasts to acquire data with extensive coverage within a few seconds. For example, typical task-related fMRI studies seek to induce different neural states in the entire brain in less than 5 s (Setsompop et al., 2016; Constable and Spencer, 2001). The current spatial resolution capability of UHF MRI in the living human brain at 7 T stands at approximately 0.8-mm isotropic resolution for functional images (Turner, 2013). While it is possible to perform laminar fMRI at 7 T or 9.4 T with higher resolution (e.g., 0.5 mm isotropic), it is still not possible to achieve it with both a short repetition time (TR) and large imaging field of view (FOV) (Huber et al., 2020). In other words, the advantage of SNR increases with UHF MRI has a trade-off with imaging spatial resolution, TR and FOV. To date, for laminar fMRI, researchers have often chosen to reduce the FOV and emphasize the spatial resolution with TR in a range of 2-5 s. For example, recent studies using BOLD contrast examined small (less than 20 % of the whole brain), straight patches of the visual cortices (Lawrence et al., 2019, 2018) and auditory cortices (De Martino et al., 2015; Moerel et al., 2019) with TRs shorter than 3.4 s. Due to the inherently low SNR of non-BOLD contrast, recent studies using non-BOLD contrast on the sensorimotor cortices (Huber et al., 2017; Yu et al., 2019) and prefrontal cortex (Finn et al., 2019) often used longer TRs than these studies with BOLD contrast. Because of these coverage constraints, nearly all the laminar fMRI studies mentioned above focused on task-related activity in a few areas. Studying laminar-specific functional connectivity (e.g., resting-state functional connectivity) is still challenging (Huber et al., 2020).

There are several hardware and sequence development approaches aimed at increasing the sampling efficiency of larger FOVs. Regarding hardware development, these include using a high-field, stronger and

(A) Magnetic field strength (3T vs 7T)



(B) Spatial resolution (2.0 mm vs 0.7 mm)





more rapidly switched, advanced head-specific RF coil and gradient coil and optimal combinations of these (Nowogrodzki, 2018; Polimeni and Wald, 2018; Stockmann and Wald, 2018). Regarding sequence development, advancing parallel imaging techniques such as SNR-efficient simultaneous multislice (SMS) and 3D acquisitions have had a high impact on improving TR and/or spatial resolution (Poser and Setsompop, 2018). Furthermore, for neuroscientists, this level of laminar fMRI technological progress represents a tipping point for considering study designs to assess the cortical laminar function of a single or a few brain areas and extending these pieces of knowledge to the whole-brain level. With the advent of large coverage laminar fMRI (Sharoh et al., 2019), the generalizability of the simplified canonical microcircuitry model needs to be considered. While the canonical microcircuit seems to be evident across the entire neocortex (Godlove et al., 2014), its universal applicability has been called into question in some cases (Constantinople and Bruno, 2013). Future insight into appropriate laminar-dependent models needs to be taken into account (Markov and Kennedy, 2013) when interpreting laminar-dependent functional connectivity data. In any case, the discovery of more complex laminar-specific pathway models of interlaminar communication further underscores the importance of high-resolution laminar fMRI for elucidating principles of the cortical connectome.

4. Hierarchical processing in the human brain: from the whole brain to layers

Human sensory processing is typically considered to occur within a hierarchical framework (Ban, 2006; Miyazaki et al., 2015; Yang et al., 2021a, 2021b, 2017, 2014, 2012; Yu et al., 2018). It is often regarded as a series of discrete processing stages across columns throughout the

Neuroscience and Biobehavioral Reviews 128 (2021) 467-478

Fig. 3. Technological advancements in human high-resolution fMRI. (A) An example of a finger tapping task conducted at 3 T and 7 T in the same subject. The higher sensitivity of 7 T relative to 3 T allows researchers to capture finger tapping-evoked brain activity in the primary motor cortex (M1) at 0.7 mm (Huber et al., 2017). (B) Conventional resolutions of 2 mm can capture tapping-induced activity in M1, while this level of resolution does not capture activity distributions across layers. In contrast, a laminar-specific double stripe pattern was identified using 0.7-mm resolution at 7 T (Huber et al., 2018b). (C) Although conventional gradient echo-blood oxygenation level dependent (GE-BOLD) contrast can capture oxygenation changes in locally nonspecific large draining veins with very high sensitivity, the local origin of the signal is unclear. The emergence of cerebral blood volume (CBV)-sensitive sequences (e.g., vascular space occupancy (VASO)) allowed mapping of activity changes with laminar localization specificity.

whole brain, and it is known to be a bidirectional hierarchy at each stage rather than being strictly bottom-up (de Lange et al., 2018; Kanai et al., 2015; Park and Friston, 2013). For example, in the visual system, visual information is initially projected to the primary visual area (V1) via the lateral geniculate nucleus (LGN), encoding basic perceptual dimensions, such as edge orientation, contrast, and local color (Fig. 5) (Groen et al., 2017, 2016; Julian et al., 2017). Then, in higher stages beyond V1, the secondary visual area (V2) and other high-level areas are considered the processing sites of higher-level visual features such as shape and textures (Epstein and Baker, 2019). Conversely, top-down feedback signals such as attention and prediction modulate the responsiveness of many areas, even the early sensory cortex, thereby enhancing perceptual sensitivity for expected stimulus features (Brandman and Peelen, 2017; Summerfield and De Lange, 2014). This bidirectional hierarchical sensory processing of the visual system may reflect the formation of a sense of context and why one can identify a "forest before trees" at a glance (Navon, 1977). Conversely, if one is allowed to view the scene long enough, one can discern more precise visual features of the "trees".

Understanding the visual system has long been a core subject in cognitive neuroscience; most human studies have mostly ignored the laminar dimension of human cortical function because of technical limitations (Kuehn and Sereno, 2018). Alternatively, electrophysiological studies in laboratory animals have provided a lens on the functional response of a small volume of neurons and facilitated understanding of the role of local microcircuits related to specific cognitive or sensory contexts (Bastos et al., 2018; Constantinople and Bruno, 2013; Hase-gawa et al., 2017; Lakatos et al., 2016; O'Connell et al., 2014; van Kerkoerle et al., 2017). Although these laboratory animal studies cannot elucidate the global context of distributed whole-brain function, they provide an essential basis for the local model of laminar-specific activity

Neuroscience and Biobehavioral Reviews 128 (2021) 467-478



Fig. 4. Schematic comparison of GE-BOLD and CBV contrasts. (A) The gradient-echo blood oxygenation level-dependent (GE-BOLD) signal is mainly sensitive to ascending veins in the tissue and pial veins (Huber et al., 2015, 2018b; Koopmans and Yacoub, 2019), which prevents precise spatial specificity to neuronal activation. (B) Non-BOLD fMRI contrasts (Bause et al., 2016; Buxton et al., 2014; Huber et al., 2014; Ivanov et al., 2017b, 2017a; Kim et al., 2013), such as cerebral blood volume (CBV), are sensitive to activation-induced redistribution of magnetization in intravascular and extravascular space. (C) The disadvantage of BOLD results in a general signal increase towards superficial layers, which may obscure the underlying laminar profiles (Huber et al., 2015). M1, primary motor cortex; CSF, cerebrospinal fluid; GM, gray matter; WM, white matter. (D) Illustrates a summary of five important quality features of GE-BOLD and CBV.



Fig. 5. Schematic of the cortical-layer to whole-brain processing hierarchies. A highly simplified example of the visual hierarchy. An early milestone laboratory animal study (Mishkin et al., 1983) revealed that the visual system is organized anatomically and functionally into two distinct pathways: the ventral and dorsal pathways. In each pathway, there are bidirectional information flows (i.e., feedforward and feedback) through the hierarchy during the corresponding visual processing. To date, this model in the visual system has been the key framework guiding visual neuroscience. However, most studies in humans have focused on brain function at the level of the whole brain or one specific visual area without considering laminar-specific cortical information processing. dlPFC, dorsolateral prefrontal cortex. IT, inferior temporal cortex. LIP, lateral intraparietal cortex.

in humans. For instance, in the much-simplified archetypal cortical circuit, layer IV (middle layer) of the primary sensory cortex (e.g., V1) directly receives sensory input and then projects these signals to neurons in layers I/II/III (superficial layers) and V/VI (deep layers) for secondary

functions of sensory information processing (right panel of Fig. 5). Moreover, layers I/II/III and V/VI are also critical for receiving feedback projections from other brain areas. Currently, this is the principle for defining cortical circuit hierarchy in the human brain, and it has been

Neuroscience and Biobehavioral Reviews 128 (2021) 467-478

adapted in many computational neuroscience studies. These studies have provided some intuitive basic cortical circuit models to help elucidate the functional roles, such as predictive coding, of neuronal populations in specific layers for human cognition (Bastos et al., 2012; Keller and Mrsic-Flogel, 2018; Lee and Mumford, 2003; Rao and Ballard, 1999). However, there is still a massive gap between what is known about the cortical circuitry from laboratory animals and models of laminar-specific activity or connectivity in the human brain. A way to overcome this fundamental issue is using laminar fMRI to test these models directly in the human brain. The current laminar fMRI technique is becoming easier to use, and the last decade has provided exciting insights at the laminar level into human brain function, as illustrated in the next section.

5. Bridging the gap between cortical circuit models and human brain function

In this section, we highlight recent laminar-specific observations in the human brain and discuss how laminar fMRI links the cortical circuit models and human brain function. We address this topic from three

(A) Feedforward and feedback effects in primary sensory cortex



(B) Hierarchical feedforward and feedback interactions in lower sensory areas



(C) Input and output in primary motor cortex



Fig. 6. The approach of defining and validating laminar-specific cortical circuit models in the human brain. (A) Laminar-specific forward and backward effects were tested in the human primary somatosensory cortex (S1) at 7 T (Yu et al., 2019). This study modified the archetypal forward-backward microcircuit model of the primary sensory cortex by considering the spatiotemporal properties of fMRI: the forward signals terminated in the middle layers, whereas the backward signals terminated in the deep and superficial layers (left panel). By manipulating the tactile sensory input and predictive backward input (middle panel), this model was validated by observing one peak activity in the middle layers for tactile input and two peak activities in the superficial and deep layers for predictive backward input (right panel). **(B)** Laminar-specific hierarchical processing across several brain areas was tested in the human visual system (Lawrence et al., 2018). The model is becoming more complex than a model of a single area because at least the direction of information flow across areas is incorporated (left panel). Consistent with the model, item-specific visual working memory (middle panel) signals activated both the superficial and deep layers but not the middle layers in V2 (right panel). **(C)** Laminar-specific input and output processing were tested in the human primary motor cortex (M1), which has different cytoarchitectonic laminar structures compared to the sensory cortex (Huber et al., 2017) (left panel). By testing the motor input and output by means of a finger tapping task either with or without finger touching (middle panel), somatosensory and premotor input in the superficial layers of M1 and corticospinal motor output in deep layers were found (right panel). Note that the laminar-specific profiles illustrated in the right panels of (A) and (C) were plotted with finer grid cortical depths, which do not represent the MRI effective resolution (i.e., 0.71 mm for A; 0.75 mm for C).

perspectives: 5.1) How can cortical circuit models be defined for laminar fMRI? 5.2) How can the structural laminar organization in the living human brain be estimated? and 5.3) How should laminar fMRI findings be interpreted?

5.1. How can cortical circuit models be defined for laminar fMRI?

Starting a laminar fMRI study with a simple cortical circuit model of a single brain region will provide researchers with an appropriate boundary and initial experimental conditions (Turner and De Haan, 2017). Despite the high spatial resolution of laminar fMRI, a submillimeter voxel of brain tissue still contains thousands of neurons (Lent et al., 2012), and the temporal resolution of fMRI has not enabled separation of the different signal types from the timing domain. It is therefore necessary to simplify the expected brain activity in units of a couple of seconds (i.e., one TR) within the smallest imaging component (i.e., one voxel) and modify the actual neuron-level model to a possible model that can be described by fMRI. For instance, in our recent study (Fig. 6A) (Yu et al., 2019), we defined a model that described sensory input signals activating middle layers of the primary somatosensory cortex (S1) to account for all thalamic and intracortical sensory input processing, whereas the feedback signals produced activity in the superficial and deep layers. A subsequent factorial designed experiment (with/without sensory input \times with/without predictive feedback) validated the model. In line with the approach mentioned above, several laminar fMRI studies have also used different types of feedback signals to determine how they modulate laminar-specific activity in the primary visual cortex (V1) (Kok et al., 2016; Lawrence et al., 2019; Muckli et al., 2015) as well as in the primary auditory cortex (A1) (De Martino et al., 2015). Overall, one can be cautiously optimistic about the principle of the middle layer of primary sensory cortices (S1, V1, and A1) receiving sensory input, while the complexity of the laminar-specific activity in superficial and deep layers requires further investigation.

It is possible to expand the basic model by adding factors such as the direction of information flow across areas to study laminar-specific hierarchical processing across several brain areas. For example, one study (Lawrence et al., 2018) aimed to measure the laminar-specific activity in three early visual areas (V1, V2 and V3) during visual working memory processing. See Fig. 6B for an illustrated model and corresponding laminar-specific activity in V1 and V2 as an example. They found that item-specific visual working memory signals activated both the superficial and deep layers while avoiding the middle layer in V1. In contrast, the item-specific working memory activity was equally strong across all layers in V2. This finding is in line with the understanding that V1 sends some sensory information to the middle layer of V2 during visual working memory processing (Self et al., 2019). However, the absolute cortical thickness of the middle layer of V2 is only half of that of V1 (Palomero-Gallagher and Zilles, 2019), and the 0.8 mm voxel in the study (Lawrence et al., 2018) was not small enough to cover the middle layer of V2 alone. While this finding may be confounded by the laminar fMRI spatial resolution and the activity across areas/layers was more complex, it provided an excellent opportunity to investigate hierarchical sensory processing at the laminar level.

The difference in cytoarchitectonic laminar structures across brain areas is also an important factor for model definition. For instance, it is widely thought that layer IV is absent in M1, which is different from that of the sensory cortex (Barbas and García-Cabezas, 2015; Palomero-Gallagher and Zilles, 2019). Therefore, it is possible to propose a simplified model of a combined superficial layer complex (layer II/III/Va) for input and a deep (layer Vb/VI) layer complex for output (left panel of Fig. 6C). In our recent study (Huber et al., 2017), we validated this motor input and output model by identifying a double-peaked activation signature in the superficial and deep layers of M1 for finger tapping accompanied by a touch task (right panel of Fig. 6C).

In addition to the cytoarchitectonic difference, an even more

complicated issue is how to define and validate a laminar-specific model of high-level cortical areas such as the prefrontal cortex (PFC), which has a central role in human cognition (Carlén, 2017). Unlike the primary sensorimotor cortices, it is not easy to modulate the balance of feedforward and feedback influences on high-level cortical areas. For example, there is strong reciprocal codependency between activity in the superficial and deep layers of the PFC during working memory tasks (Bastos et al., 2018), making it difficult to assess the difference in activity across layers. Our recent study (Finn et al., 2019) provided a promising demonstration that laminar-specific activity in the human dorsolateral PFC can be separated by manipulating the working memory task requirement for different epochs. Specifically, we found that the superficial layers of the dorsolateral PFC are preferentially active during the delay period, whereas the deep layers are preferentially active during the response period. Understanding the laminar-specific role of the high-level cortical areas is necessary to yield new insights into human cognition (Finn et al., 2020), which will require improved laminar fMRI techniques and well-designed experimental paradigms.

The future direction to improve the laminar-specific cortical circuit model definition requires further cross-species validations (i.e., humans and NHPs) and cross-methodology validations (i.e., laminar fMRI and other invasive methods). All the human laminar fMRI studies mentioned above defined their models dependent on NHP findings, which were not quantitatively validated across species and across imaging and analysis methodologies. Therefore, these findings fall short of interpreting the laminar-specific fMRI signal in terms of neural activity that underlies the diversity of human cognition. To overcome this limitation, a multimodal imaging technique combining laminar fMRI with invasive neurophysiological and/or optogenetic measures in NHPs can establish the relationships between fMRI signals and neural activity. Then, one can employ the same laminar fMRI method used in NHP studies in humans by means of cross-species computational modeling, which would provide a common description of neural activity from fMRI signals in the human brain.

5.2. How can the structural laminar organization in the living human brain be estimated?

Typical fMRI studies have to take a few minutes to acquire a highresolution structural image (e.g., T1-weighted image) to provide a basis for anatomical references of brain activity. Regarding brain function at the laminar scale, estimating the structural laminar organization in the living human brain has become a crucial question (Turner, 2013). The spatial resolution of UHF MRI can be as high as 0.3 mm for structural images, which can show layers of myelinated axons within the living human cerebral cortex and potentially direct assessment of the cortical thickness of each layer (Amunts and Zilles, 2015; Fukunaga et al., 2010; Trampel et al., 2019). However, a practical limitation regarding the use of UHF MRI to estimate cortical myelin patterns is that small head motion (e.g., 0.5 mm) and image artifacts will obscure the details of the cortical laminar structure. Nevertheless, a 0.3-mm voxel is larger than the thickness of individual layers (which are between 0.1 and 0.8 mm (Wagstyl et al., 2020)), leading to partial volume effects in which voxels contain multiple layers. Thus, in vivo UHF MRI alone is not yet suitable to provide precise mapping of cortical layer thickness. A potentially fruitful approach to overcoming this issue is to quantitatively compare the in vivo living human MRI data to cadaver brain ex vivo MRI data and histological data (Fig. 7) (Huber et al., 2017; Turner, 2013). At present, one can obtain ex vivo cortical layer data (Wagstyl et al., 2020) at 20-micrometer isotropic resolution of the human brain (BigBrain) from the Human Brain Project at https://www.humanbrainproject. eu/en/explore-the-brain/atlases/. Beyond this approach, recent studies (Dinse et al., 2015; Waehnert et al., 2014) have provided evidence showing that combining models of laminar myelin patterns based on known cytoarchitecture is expected to improve the quality of cortical layer localization. While these approaches are well intentioned, to the



(C) Standardized MRI signal profiles of postmortem ex vivo MRI and in vivo MRI data



Fig. 7. Cortical layer assignment by comparison between *ex vivo* **high-resolution postmortem and** *in vivo* **data. (A)** Postmortem histological and T1 MRI data identifying laminar landmarks. Layers 5a and 5b of the primary motor cortex (M1) can be identified through a plateau of the T1 image with indication of two subpeaks (red arrows) (Huber et al., 2017). **(B)** These landmarks are also visible in the *in vivo* data of living humans. **(C)** The "knee-point" (brown arrow) is used as a laminar landmark for the approximate position of layer 5a in the functional results.

extent that we classify the cortical layers by combining the data with different individuals and/or different imaging modalities, the layer classification accuracy can be influenced.

5.3. How should laminar fMRI findings be interpreted?

A solid grounding in the potential and limitations of fMRI is required to draw precise conclusions from laminar fMRI data. Because an exhaustive overview of the basis of fMRI is beyond the scope of this review, we highlight only a few critical points in the context of hemodynamic responses, data acquisition and data analysis that would help researchers avoid laminar fMRI data overinterpretation.

FMRI is an indirect measure of brain activity, as it is based on the hemodynamic effects related to local neural activity. A large number of laminar fMRI studies (for details, see review (Poplawsky et al., 2019)) in laboratory animal models have indicated that the hemodynamic responses measured by fMRI reflect the neuronal activity determined by vascular physiology and MRI physics. For example, the fMRI signal from a specific layer will be affected by the blood carry-over effect towards the cortical surface by the microvascular distribution across layers (Uludağ and Blinder, 2018); thus, care should be taken to draw conclusions based on comparing the activation amplitude across layers in one condition. The temporal specificity of fMRI signals is restricted by the temporal properties of hemodynamic responses. In theory, laminar fMRI allows us to capture a submillimeter voxel of brain tissue within a second; however, neuronal activity spreads across layers much faster (i. e., a few ms) than the onset and spread of hemodynamic responses (i.e., a few 100 ms) (Petridou and Siero, 2019). Thus, the temporal variability across layers results in voxel-specific fMRI signal changes that need to be taken into account. Aside from these points, an understanding of the basic properties of hemodynamic responses is also essential to reach

correct conclusions (for details, see review (Logothetis, 2008)).

The partial volume effect arises in fMRI, resulting in another potential data overinterpretation. For fMRI imaging, the term partial volume effect mostly refers to partial signal contamination from two distinct stages: data acquisition and data analysis. During data acquisition, even a submillimeter laminar fMRI voxel contains signals from multiple cytoarchitectonic layers. During the data analysis, the partial volume of multiple voxels with variable centroids was used to reconstruct layers. Thus, to minimize partial volume contamination caused by layer reconstruction during data analysis, many of the laminar fMRI studies (Kok et al., 2016; Lawrence et al., 2019, 2018) have preferred to draw their conclusions in terms of three "lavers"-deep, middle, and superficial-which are close to the raw spatial resolution (approximately 0.8 mm). In the future, researchers can take advantage of this strategy for interpreting the data at the actual spatial level while minimizing partial volume contamination during data acquisition by increasing the spatial resolution. To date, due to technical limitations of fMRI, one potential solution to increase spatial resolution is to record anisotropic data by increasing the resolution perpendicular to layers while increasing the thickness in other directions (Kashyap et al., 2018). However, the choice of high-resolution direction is dependent on the anatomical structure of the cortex, and it is challenging to adapt this approach to high-level areas that are highly variable across individuals (Mueller et al., 2013). An alternative approach is tolerating the fact of partial volume contamination caused by data acquisition while correcting it by upsampling the raw data to a proper finer spatial grid (Finn et al., 2019; Huber et al., 2017; Muckli et al., 2015; Polimeni et al., 2010; Yu et al., 2019) and/or adapting the model (van Mourik et al., 2019). For example, with a cortical thickness of 4-5 mm in human M1, we found that a grid of twenty layers (approximately four times larger than the raw spatial resolution) significantly reduces the partial volume

contamination (Huber et al., 2018b). However, this approach still has its challenges. For example, the neighboring data points in the upsampled layers are not statistically independent, and the difference in algorithms of assigning layers to cortical depths may cause segmentation errors. To date, no concrete segmentation algorithm has been published; thus, laminar fMRI researchers still need to manually check each dataset for errors. Even the partial volume issue could be alleviated by improving the effective spatial resolution in the future, the problem will not go away.

In addition to these limitations based on fMRI, noise from various sources, including subject motion and subject physiology, confounds the imaging quality, which becomes a crucial question at the laminar scale (Huber et al., 2018a; Hutton et al., 2011). Existing strategies rely on post hoc motion correction combined with different regression techniques (Power et al., 2015), which can make it challenging to estimate correction accuracy. To date, there is still no consensus on optimal methods to remove motion artifacts, and it is difficult to identify the "ground truth" of what signals ought to be removed. Furthermore, involuntary cardiac pulsation also becomes an issue at laminar resolutions. For example, cardiac- and respiration-induced signal fluctuations have been shown to result in signal changes in task-related and resting-state fMRI (Birn et al., 2009, 2006), while task-related fMRI studies complemented by parallel physiological monitoring remain in the minority. The current noise removal trend with high-resolution image acquisition (e.g., 0.7 mm isotropic) is to apply the recorded physiological parameters or data-driven noise removal model during data analysis (Polimeni et al., 2018). Recently, the advantage of the new approach combining spatial independent component analysis (ICA) (for motion artifacts) and temporal ICA (for physiological artifacts) for denoising both task-fMRI and resting-state data has been demonstrated (Glasser et al., 2018). Future laminar fMRI data denoising will benefit from such new methods.

In conclusion, considering all these advantages and disadvantages together, recent findings have provided evidence validating that laminar fMRI techniques can be used to map laminar brain activity, but not without difficulties (for additional methodological considerations of laminar fMRI, see review articles (Bollmann and Barth, 2020; Goense et al., 2016; Moerel et al., 2020; Weldon and Olman, 2021)). In the future, the combination of *in vivo* laminar fMRI with other *ex vivo* imaging techniques and the parallel use of more direct measures from laboratory animal models will be the most effective way to understand human cognition at the laminar level.

6. Concluding remarks and future perspectives

A better understanding of the cortical layers in the human brain will help in determining the laminar-specific functional activity underlying human cognition. The development of tools for observing laminarspecific activity in the living human brain is fundamental to advancement in this field. BOLD and non-BOLD laminar fMRI in UHF MRI systems have been developed and are still evolving. In this article, we discussed the advantages and limitations of laminar fMRI and suggested how to use the method to answer specific scientific research questions.

One clear benefit of the laminar fMRI technique is its high spatial resolution, which has opened a new dimension (cortical depth direction) for examining the neural basis underlying human cognition. Furthermore, it has revealed the potential to clarify cortical hierarchy, causality, and connection directionality. However, laminar fMRI has limitations. For instance, the fMRI spatial resolution directly affects the scan duration and imaging coverage. In theory, one can produce images that cover the entire brain using very high spatial resolutions (e.g., 0.1 mm) with UHF MRI scanners; however, it would not be practically feasible for many reasons, including the extremely low SNR (Turner and De Haan, 2017), image stability, and the necessary time for acquisition. A critical aspect of improving laminar fMRI is the development of either novel acquisition and contrast sensitivity, as well as embracing new

hardware developments that include RF and gradient coils. In addition to these methodological improvements, another relevant challenge for laminar fMRI is the lack of a robust standardized data analysis pipeline. Several neuroimaging data analysis pipelines, such as FreeSurfer (http: //surfer.nmr.mgh.harvard.edu/) and AFNI (http://afni.nimh.nih.gov/), as well as some in-house code scripts, are starting to be optimized for laminar fMRI data (Huber et al., 2021).

From the basic science perspective, the routine use of laminar fMRI would complement electrophysiological laboratory animal research by providing more direct insights into the relationship between brain activity at the laminar level and human cognition. Recent laminar fMRI studies have made an important new step in linking cortical circuit models to human cognition. Several scientific questions remain. For instance, in cases when the activity patterns across layers match the expected laboratory animal-based cortical circuit models, can one conclude that a specific brain area plays the same functional role in humans as in laboratory animals? Often, the answer to this question is no. While the basic cytoarchitecture and neuronal physiology of the brain are similar across primates, they can still differ in some respects, especially in terms of cortical volume and neuronal density (Somel et al., 2013). To resolve this class of problems, an important direction for future work will be more extensive and exhaustive cross-species and cross-modality comparisons at the laminar level.

Finally, to meaningfully interpret laminar-specific hierarchical processing in the human brain, it is essential to appreciate and embrace the idea of functional connectivity across layers (Larkum et al., 2018; Sotero et al., 2015, 2010). Addressing these challenges using careful and iterative comparisons of human and laboratory animal models along with well-constructed computational models will help to further lay the groundwork for elucidation of the underpinnings of human cognition.

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