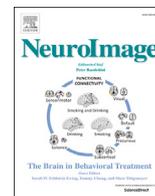




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Laminar fMRI: Applications for cognitive neuroscience

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ABSTRACT

The cortex is a massively recurrent network, characterized by feedforward and feedback connections between brain areas as well as lateral connections within an area. Feedforward, horizontal and feedback responses largely activate separate layers of a cortical unit, meaning they can be dissociated by lamina-resolved neurophysiological techniques. Such techniques are invasive and are therefore rarely used in humans. However, recent developments in high spatial resolution fMRI allow for non-invasive, in vivo measurements of brain responses specific to separate cortical layers. This provides an important opportunity to dissociate between feedforward and feedback brain responses, and investigate communication between brain areas at a more fine-grained level than previously possible in the human species. In this review, we highlight recent studies that successfully used laminar fMRI to isolate layer-specific feedback responses in human sensory cortex. In addition, we review several areas of cognitive neuroscience that stand to benefit from this new technological development, highlighting contemporary hypotheses that yield testable predictions for laminar fMRI. We hope to encourage researchers with the opportunity to embrace this development in fMRI research, as we expect that many future advancements in our current understanding of human brain function will be gained from measuring lamina-specific brain responses.

1. Introduction

Neural activity in a given brain area depends on a combination of bottom-up drive and feedback modulatory processes (Bastos et al., 2012; Heeger, 2017; Muckli, 2010; Roelfsema and De Lange, 2016). Higher-level cognitive processes modulate responses in lower-level, sensory brain regions, facilitating the analysis of incoming sensory data. The interaction between top-down and bottom-up signals in sensory cortices is a fast-growing and increasingly important area of research for cognitive neuroscience. At standard imaging resolutions, however, fMRI responses comprise an amalgamation of both bottom-up and top-down responses (Dumoulin et al., 2017a; Harris and Mrsic-Flogel, 2013; Rockland and Pandya, 1979). Most research distinguishing between bottom-up and top-down functional signals has been performed on non-human primates using so-called laminar electrodes (Self et al., 2013; Van Kerkoerle, Self and Roelfsema, 2017), where multiple contact points, spaced 100 micrometers apart, allowed for the simultaneous recording of multiunit neural activity and current-source density at different cortical depths. Layer-specific imaging is also performed in rodents by recording dendritic Ca^{2+} activity at different cortical depths (Takahashi et al.,

2016). The invasive nature of these measurements makes their application in humans challenging. However, recent developments in high spatial resolution fMRI (Dumoulin et al., 2017a; Koopmans et al., 2010, 2011) provide an exciting opportunity for in vivo measurements of lamina-specific activity in humans. Laminar fMRI, therefore, may provide researchers with a tool for distinguishing bottom-up and top-down cortical responses, and examining the interactions between the two.

In the current paper, we will highlight some recent successful applications of laminar fMRI and provide an outlook of how laminar fMRI could open up new avenues of research and lead to a deeper understanding of how the brain implements various cognitive functions to aid perception. We thereby hope to generate enthusiasm for this challenging but rewarding new field of research.

2. Characterizing fMRI responses and receptive field characteristics across cortical depths

Before inferences can be made from laminar fMRI about neural activity across cortical depths, one must first understand how the relationship between neural activity and the vascular changes measured with

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fMRI, or neurovascular coupling, varies as a function of cortical depth. Early laminar fMRI studies identified that the visually driven BOLD response in human visual cortex exhibits a steady increase towards the cortical surface (Ress et al., 2007). However, this was likely due to large signals arising from venous blood draining towards the pial surface (Turner, 2002). Correcting for the contribution of venous draining reveals a peak in the visually driven BOLD response in layer 4 of V1 (Koopmans et al., 2010), as would be expected from invasive recordings from animals (Hubel and Wiesel, 1972). Goense, Merkle and Logothetis (2012) carefully examined neurovascular coupling across cortical depths using laminar fMRI measurements of changes in BOLD, cerebral blood volume and blood flow in stimulated and unstimulated regions of macaque V1. Neurovascular coupling was found to vary both depending on whether the cortex was stimulated and across cortical depths. This should therefore be taken into account when making inferences about neural activity from laminar fMRI responses (see Uludağ and Blinder, 2017; for review). Challenges regarding the spatial specificity of laminar fMRI and how they may be overcome are further discussed later in this review.

Other studies have used laminar fMRI to examine changes in receptive field properties across cortical depths. Fracasso, Petridou, and Dumoulin (2016) identified smaller population receptive field sizes in middle layers of visual cortex compared to deeper and superficial layers, consistent with invasive measurements of animals for receptive field size and orientation tuning width (Self et al., 2013). Advancements in high resolution imaging have also allowed for in vivo measurements of human columnar cortical structures. Ocular dominance columns were first successfully imaged in human V1 (Cheng et al., 2001; Yacoub et al., 2007), followed by orientation columns (Yacoub et al., 2008). Dumoulin et al. (2017b) extended the method beyond V1, identifying columnar structures in the stripes of V2 and V3. Finally, De Martino et al. (2015)

successfully imaged columnar structures exhibiting frequency tuning in the primary auditory cortex. Together, these examples demonstrate that high spatial resolution fMRI can provide important insights into neural response properties across cortical depths, and columnar structures of the human brain.

3. Forward, backward, and lateral message-passing within the neocortex

The neocortex is a massively recurrent network, characterized by feedforward connections between areas (e.g., between primary visual area V1 and secondary visual area V2) that are complemented by feedback connections (in a ratio of ~1:1), as well as lateral connections within an area. Although most information processing is local and contained within a cortical column (Binzegger et al., 2004), the response of a neuron can be strongly modulated by lateral and feedback connections (Angelucci et al., 2002; Gilbert and Li, 2013; Muckli and Petro, 2013). Neocortex can be divided into six layers on the basis of histological data. Feedforward, horizontal, and feedback processes activate different layers of a cortical unit (Self et al., 2013; see Fig. 1C). For example, feedforward connections into V1 from the lateral geniculate nucleus of the thalamus primarily terminate in layer 4 (Hubel and Wiesel, 1972). Lateral connections between V1 columns are present in all layers but predominantly terminate in upper layer 4 and the superficial layers (Rockland and Pandya, 1979). Finally, feedback connections from higher visual areas terminate primarily in layers 1 and 5 and avoid layer 4 (Anderson and Martin, 2009; Felleman and Van Essen, 1991; Markov and Kennedy, 2013; Rockland and Virga, 1989). This relatively distinct organization of feedforward and feedback connectivity allows for a potential spatial separation of feedback and feedforward activity modulations, which are

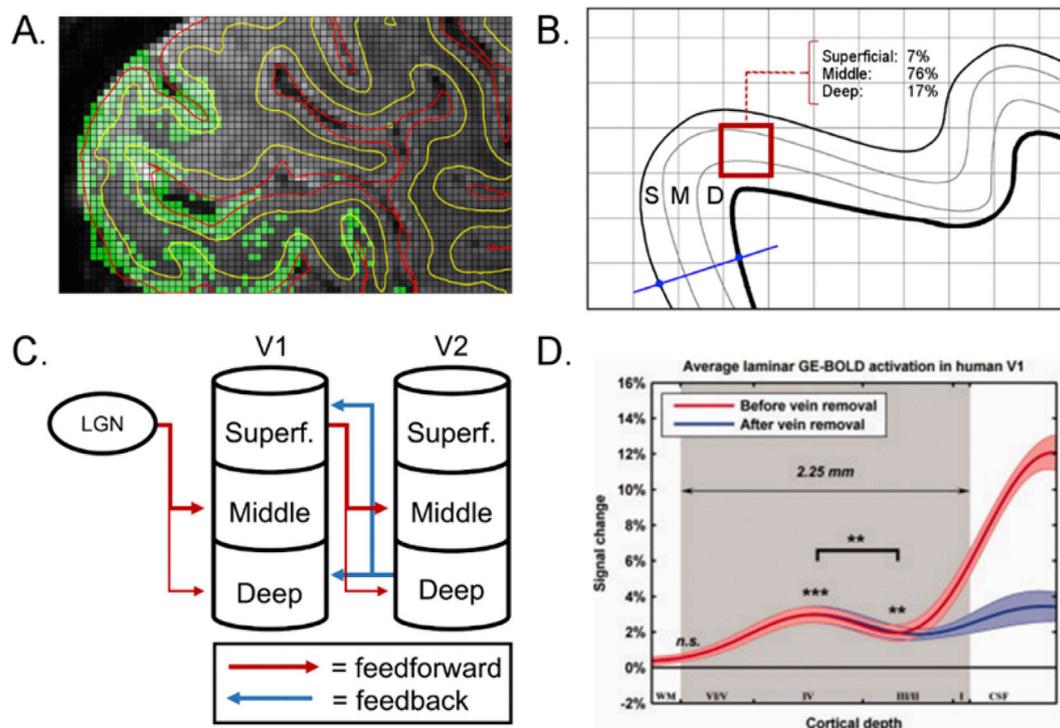


Fig. 1. (A) Sagittal slice of a functional volume acquired using a T2*-weighted 3D gradient-echo EPI sequence. The black grid shows the size and location of 0.8 mm isotropic functional voxels. Gray-white matter (yellow line) and gray matter-CSF (red line) boundaries are overlaid onto the volume, showing the distribution of functional voxels across cortical depths. (B) Schematic representation of a functional voxel (red square) and its distribution of three gray matter layers. These layer weights can be used as the basis of a regression approach to obtain layer-specific BOLD responses (see Kok et al., 2016; for more information). (C) Schematic representation of the feedforward (red arrows) connections between human LGN, V1 and V2 and feedback (blue arrows) connections between V1 and V2. V1 and V2 are split into superficial, middle and deep gray matter layers to demonstrate how laminar fMRI can be used to estimate feedforward and feedback responses by measuring layer-specific responses. For clarity, only intercolumnar and not intracolumnar connections are represented. (D) BOLD activation profile in human V1 across cortical depths. Of note is the peak in activation in input layer 4 (labelled IV) and the large signal increase towards the cortical surface and into the CSF (red line) caused by large signals from venous draining towards the pial surface. Masking out voxels that overlap with venous structures before analysis removes this artifact from the data (blue line). Panels A and B were reproduced with permission from Kok et al. (2016) and panel D was reproduced with permission from Koopmans et al. (2010).

thought to have distinct functional roles (Self et al., 2013). At present, the spatial resolution of laminar fMRI is not sufficient for imaging of individual cortical layers. Therefore, studies using laminar fMRI have typically divided gray matter into several evenly spaced bins, as an approximation of the underlying cortical laminae (Fig. 1A and B). Consistent with the known functional architecture of the cortical column, these studies find feedback responses in deep and superficial, but not middle, cortical bins (De Martino et al., 2015; Kok et al., 2016; Muckli et al., 2015; Scheeringa et al., 2016).

4. Visual prediction

Influential neurocomputational models of cortical function posit that feedforward filtering operations are complemented by feedback processes that carry a generative model (or prediction) of expected input (Friston, 2005; Heeger, 2017; Lee and Mumford, 2003). Two recent studies examined the laminar profile of activity patterns in V1 under conditions of expected but absent bottom-up input. Muckli et al. (2015) used laminar fMRI to measure contextual influences on visual cortex responses to a visual scene where part of the image was masked by an occluding object. The content of the surrounding visual scene was successfully decoded from patterns of activity in regions of visual cortex whose receptive fields fell on the occluded part of the image. However, decoding was only successful in the superficial layers of these cortical regions. This suggested that information about the surrounding scene was represented in areas of visual cortex that received no bottom-up input, via feedback mechanisms terminating in the supragranular layers. Kok et al. (2016) measured the top-down elicited activity in V1 during perception of the famous Kanizsa triangle illusion (Kanizsa, 1976; Kok and De Lange, 2014) with laminar specificity. Positive responses to the illusory shape were only present in the deep layers of V1, whereas a physical stimulus activated all layers. Therefore, the perception of illusory shape may result from processing in higher-level brain regions that form a prediction to explain the shape inducers and feed the prediction back to the infragranular layers of V1. The differences in feedback effects between these studies could have many origins. Firstly, they could be due to differences in methods: Kok et al. (2016) used a spatial regression approach to estimate layer-specific mean BOLD responses, while Muckli et al. (2015) quantified how well contextual information from occluded stimuli could be decoded on the basis of multivariate patterns of BOLD activation/de-activation. In the Muckli study, BOLD activation from visually stimulated cortex increased towards the outer pial surface, and multivariate pattern classification plateaued. In occluded conditions, mean BOLD activity did not increase towards the pial surface, but multivariate decoding accuracy did. In another study, decoding accuracy from gradient echo BOLD data has been shown to improve towards superficial layers (Moerel et al., 2017), due to increased signal intensity from venous draining towards the pial surface (Fig. 1D). However, Muckli et al. (2015) also observed better decoding in superficial layers with a 3D GRASE sequence, which is less susceptible to venous artifacts (De Martino et al., 2013). Finally, it is also possible that the two contextual feedback effects operate via separate mechanisms with different laminar terminations in V1. For example, feedback during image occlusion (amodal completion) may only induce a small activation fluctuation in superficial layers while illusory contours (modal completion) may constitute a stronger illusion that triggers suprathreshold activation in deep layers of cortex. There is a neuronal mechanism known to integrate apical dendritic signals in superficial layers with more proximal dendrites in deep layers (Takahashi et al., 2016). Therefore, increased apical amplification (Phillips et al., 2016) during the Kanizsa illusion could result in different activation intensities in superficial and deep layers of V1. In any case, both studies are consistent with the known functional neuroanatomy of feedback projections which terminate in superficial and deep layers, but avoid layer 4 (Anderson and Martin, 2009; Rockland and Virga, 1989).

Together, these studies demonstrate how laminar fMRI can be used to

tease apart bottom-up and top-down signals in visual cortex in the context of visual prediction. There are many other examples of cognitive processes that influence sensory responses and perception; in the following sections we will discuss some of these processes and how laminar fMRI might be used to shed new light on their respective fields of research.

5. Working memory and mental imagery

Short term memory of a visual object is thought to be achieved through the recruitment of sensory brain regions involved in perceiving that object, as higher-level brain regions commonly associated with memory lack the visual selectivity to represent specific visual features (Pasternak and Greenlee, 2005). Similarly, mental imagery might involve the recruitment of early visual cortex as a ‘cognitive blackboard’, with higher areas inducing virtual sensory data in V1 to represent an imagined stimulus (Roelfsema and De Lange, 2016). These hypotheses are supported by brain decoding studies, which show that patterns of activity across early visual cortex during the maintenance of a previously presented grating stimulus (Harrison and Tong, 2009; Serences et al., 2009) or an internally imagined one (Albers et al., 2013) are similar to patterns induced by bottom-up perception of the same stimulus. Moreover, in the study by Albers et al. (2013) a decoder trained on patterns induced during memory was equally accurate in decoding the orientation of an imagined grating as a classifier trained on patterns induced by perception, implying that representations of memory and imagery may be formed by the same perceptual mechanisms (Tong, 2013).

Though the perception, memory and imagination of the same stimulus result in similar patterns of activity across visual cortex as measured at standard fMRI resolutions, laminar fMRI could reveal differences between patterns in terms of their laminar profiles. That is, a single orientation column might yield a similar overall response during the perception, memory and imagination of its preferred orientation, but the contributions of input and feedback layers to the overall response are likely to be different in each case. Recent electrophysiology data support this idea. Van Kerkoerle et al. (2017) recorded neuronal responses from different layers of macaque V1 during a curve-tracing task where, in some trials, the target curve was removed for a delay period so the monkey had to remember the location and arc of the target curve. Neurons in superficial and deep layers of V1 whose receptive fields fell on the location of the target curve increased their firing rates during this delay period. In contrast, when the target curve was visually presented increased firing rates originated in input layer 4. Similarly, another study finds that only neurons in deep layers of macaque temporal cortex increase their responses during active retrieval of a visual stimulus (Koyano et al., 2016). These studies demonstrate that although, at a broad scale, visual working memory involves some of the same brain regions as visual perception, at a finer scale the laminar profiles of responses during perception and memory are quite different. Laminar fMRI can be used to extend these findings to humans, revealing which layers contribute to successful decoding of visual stimuli during working memory and mental imagery. In addition, the hypothesis that working memory and mental imagery operate via the same mechanisms (Albers et al., 2013; Tong, 2013) could be explicitly tested, as it predicts that the laminar profiles of working memory and imagery responses should be the same. Some of the authors (SJD and FPL) are actively pursuing this research question at present.

6. Selective attention

One of the most important ways that we can influence our processing of sensory stimuli is through directing our attention towards a desired spatial location or object feature. This results in an enhanced neural representation of the attended location or feature, optimizing the allocation of neural resources. Spatial and feature-based attention have been shown many times to modulate responses throughout the visual cortex

(Buracas and Boynton, 2007; Carrasco, 2011; Kamitani and Tong, 2005), though reports of attentional modulations in V1 are mixed (Boynton, 2011; Yoshor et al., 2007). Attentional modulations comprise feedback effects from a network of attentional control brain regions including the frontal eye fields, dorsomedial prefrontal and posterior parietal cortices (Corbetta and Shulman, 2002; Kastner and Ungerleider, 2000) as well as modulations from subcortical structures (Shipp, 2004). Effects of attention in sensory cortex, therefore, could be expected to be most pronounced in superficial and deep layers, where feedback projections terminate (Anderson and Martin, 2009; Rockland and Virga, 1989). Indeed, a combined human laminar fMRI and EEG study found that BOLD responses in superficial and deep layers of early visual cortex covaried with EEG oscillations that occurred in response to an attentional task manipulation (Scheeringa et al., 2016). Furthermore, another laminar fMRI study shows that frequency tuning curves in human primary auditory cortex sharpen towards an attended tone, and that this sharpening is more pronounced in superficial compared to other layers (De Martino et al., 2015). Together, these examples demonstrate how laminar fMRI can be utilized to better characterize the nature of feedback effects from high-level attentional control brain regions in sensory cortices.

One intriguing avenue for future laminar fMRI research could lie in characterizing the laminar profiles of both positive and suppressive effects of attention. Spatially-directed attention both enhances responses to the attended location and suppresses responses to unattended locations (Gouws et al., 2014; Smith et al., 2000). For example, Gouws et al. (2014) showed that directing attention towards one visual hemifield elicited positive BOLD responses in contralateral visual cortex and negative responses in ipsilateral visual cortex. Moreover, positive and negative BOLD responses in visual cortex were mirrored by positive responses in the dorsolateral pulvinar and negative responses in the dorsomedial pulvinar, respectively. The pulvinar is frequently implicated in attention, and shares feedforward and feedback connections with many regions throughout cortex (Shipp, 2003). This led Gouws et al. to the hypothesis that the pulvinar is the source of an attentional field (Reynolds and Heeger, 2009) that modulates responses in visual cortex. This hypothesis can be tested using laminar fMRI, with the prediction that positive modulations originate in dorsolateral pulvinar, which projects primarily layers 3 and 4 of occipital cortex (Shipp, 2003), while negative modulations originate in dorsomedial pulvinar, which projects primarily to parietal cortex (Behrens et al., 2003; Gutierrez et al., 2000) and then to feedback layers of visual cortex. Interestingly, one recent study found that increased neuronal firing rates from spatial attention were significantly stronger in input layer 4 of macaque V4 compared to other layers (Nandy et al., 2017), providing some support for this hypothesis. Overall, attentional modulations of sensory responses clearly involve a complex communication between a large network of brain areas (Shipp, 2004), making it ripe for further investigation of feedforward and feedback responses with laminar fMRI.

7. Visual saliency

The attentional mechanisms described above exert influence over sensory processing systems via top-down cognitive control. However, attention can also be allocated automatically to surprising or unexpected stimuli via bottom-up mechanisms, efficiently boosting the representation of highly salient visual stimuli (Nakayama and Mackeben, 1989). Bottom-up attention is thought to be controlled by a visual saliency map in the brain, which reports the saliency of all locations in the visual field (Koch and Ullman, 1985). Visual saliency is not dependent on what feature defines an objects salience, leading to the dominant view that the saliency map likely resides in the parietal cortex where neuron receptive fields are not selective for specific visual features (Itti and Koch, 2001; Koch and Ullman, 1985). In contrast, Li (1999, 2002) proposed that V1 forms a bottom-up saliency map that is propagated through the visual hierarchy. In this model, the saliency of a visual location is proportional

to the net response of V1 neurons responsive to that location, irrespective of their preferred visual feature. Zhang et al. (2012) provide evidence to support this hypothesis. Their study found that BOLD responses in V1-V4, but not parietal cortex, increased with the saliency (determined by a behavioural attentional cueing effect) of a stimulus rendered invisible by rapid presentation and backward masking. Importantly, the use of an invisible stimulus allowed Zhang et al. to isolate the automatic, bottom-up visual response from top-down, attentional modulations. Li's (1999, 2002) V1 saliency map hypothesis can be explicitly tested using laminar fMRI. The hypothesis predicts that bottom-up attentional modulations to an invisible stimulus should have a dissociable laminar profile from top-down modulations. That is, top-down effects of attention should be more potent in the superficial and deep layers of visual cortex, where feedback projections are most prominent (Anderson and Martin, 2009; Rockland and Virga, 1989), compared to bottom-up effects of visual saliency. The notion of a saliency map in V1, therefore, is another example of a hypothesis that yields testable predictions for laminar fMRI.

8. Multisensory integration

In the cortex, sensory areas may interact through several possible pathways, which are not mutually exclusive. For example, auditory stimulation can elicit specific activation patterns in human early visual cortex (Petro et al., 2017; Vetter et al., 2014). Influences from one sensory area to the other may arrive in form of feedback projections from multisensory areas (Felleman and Van Essen, 1991) or projected through non-specific thalamic afferents, which are essentially feedforward projections (Van Atteveldt et al., 2014). In addition, there is accumulating evidence that early sensory cortices interact via direct cortico-cortical pathways. Recently, Ibrahim et al. (2016) were able to trace, in the mouse, the direct axonal projections from the primary auditory cortex, A1, to V1 (but not the reciprocal connections, i.e. from V1 to A1). The strength of the A1 to V1 projection was maximum in layer 1 of V1 and originated mostly from layer 5 of A1. This same study showed that neurons in V1 layer 1 are activated either by sound or by optogenetic stimulation of A1-V1 axons and that - as a consequence of the inhibitory effects of layer 1 neurons - the orientation tuning of layer 2/3 pyramidal neurons was sharpened (Ibrahim et al., 2016). That influences from other senses affect especially supragranular layers of the receiving area is also consistent with findings outside V1. For example, in awake macaque monkeys, Lakatos et al. (2007) found a strong influence of somatosensory inputs in the supragranular layers of A1. However, other reports are inconsistent with this hypothesis. For instance, laminar recordings in rats localized the correlates of a learned audiovisual association (tones and light) in infragranular V1 layers (layers 5 and 6; Headley and Weinberger, 2015). With laminar fMRI, these fundamental mechanisms and the neuronal pathways underlying multisensory interaction and interareal communication can be investigated in the human brain. This is highly relevant as predictions from animal models are not unequivocal and prominent differences between species may exist. It will be important to combine laminar fMRI with psychophysical paradigms that enable the online measurement of behavior. If indeed the supragranular layers of V1 do mediate the integration of information from other senses (e.g. A1), the modulation of fMRI activity in supragranular V1 should scale, trial-by-trial, with the facilitatory effects of, for example, informative auditory stimuli on visual target detection (e.g. Vroomen and de Gelder, 2000).

9. Consciousness

One of the central questions in cognitive neuroscience is how consciousness emerges from neural processes (Crick and Koch, 2003). In particular, what roles do low-level sensory systems play in conscious perception? That is, do neural signals in primary sensory processing regions reflect the physical properties of the world or our conscious perception of it? Reports regarding the role of primary visual cortex in conscious vision have been mixed, with some reporting V1 responses

reflect perceived reality (Kok and De Lange, 2014; Muckli et al., 2005; Murray et al., 2006; Watkins et al., 2006), while others report a better match with physical reality (Crick and Koch, 1995; Haynes and Rees, 2005; Mikellidou et al., 2016). However, patients suffering from blindsight (Azzopardi and Cowey, 1998; Weiskrantz, 1996) following a lesion to V1 offer compelling evidence that V1 is necessary for conscious visual perception. Blindsight patients suffer from total blindness, and yet can perform at above chance levels on some visual tasks, without awareness that they are doing so (Stoerig and Barth, 2001; Stoerig and Cowey, 1992, 1997). In addition, lesions to category-selective areas of visual cortex such as color- and motion- selective cortex cause color (Zeki, 1990) and motion blindness (Zeki, 1991), respectively, suggesting these regions are necessary for conscious vision of specific visual features. These case studies can be reconciled by interactive models of consciousness (Tong, 2003), which propose that communication between high- and low-level brain areas is the key to awareness. Consistent with this, recent evidence from rodent Ca^{2+} imaging suggests that the cortical feedback to apical dendrites of layer 5 pyramidal cells play a key role in conscious perception of whisker stimulation (Phillips et al., 2016; Takahashi et al., 2016). Due to their emphasis on interactions between bottom-up and top-down mechanisms, interactive models of consciousness yield testable predictions for laminar fMRI.

According to interactive models, top-down signals from high-level brain areas to lower-level sensory areas are necessary for conscious sensory perception (Bullier, 2001; Lamme and Roelfsema, 2000; Pollen, 1999). Therefore, a visually perceived stimulus should be represented by both bottom-up and top-down responses in visual cortex. Moreover, a visual stimulus that is not perceived should not induce top-down responses to visual cortex. These predictions can be explicitly tested with laminar fMRI. For example, Haynes and Rees (2005) showed that the orientation of a grating stimulus rendered invisible by brief presentation and backward masking could be decoded from patterns of activity in V1. Interactive models of consciousness predict that information about the visually presented stimulus that does not reach awareness should not be met by top-down responses from higher-level brain areas. This predicts, therefore, that information about an invisible stimulus should be present in the middle input layers of V1, but not the superficial and deep feedback layers (Anderson and Martin, 2009; Rockland and Virga, 1989). The emergence of consciousness is clearly a complex issue that is far from being fully understood, however interactive models that emphasize the importance of communication between brain areas yield testable predictions for laminar fMRI that could advance the field.

10. Hallucinations and delusions

It is contemporary theory that schizophrenia, a mental disorder with symptoms including hallucinations and delusions amongst others, is linked to abnormal predictive coding mechanisms (Fletcher and Frith, 2009). As described earlier in this review, predictive coding is a compelling account of neural processing in which high-level brain systems form a world model that best explains the incoming sensory data (Bastos et al., 2012; Friston, 2005). Sensory brain areas communicate the error between the current model and sensory input to higher-level areas, which in turn adjust the model and feed the new model back to sensory areas. Evidence suggests that hallucinations and delusions are not linked to impaired reasoning (Kemp et al., 1997), but are instead linked to abnormal perception (Maher, 1974). That is, patients may experience unusual perceptions due to abnormal modulations of responses to predictable, unimportant or self-generated stimuli, and erroneous activation of sensory cortex. Delusions may follow as the current world model is adjusted to account for hallucinations or abnormal perceptions, leading to unusual beliefs (Fletcher and Frith, 2009). Consistent with this, patients who suffer from hallucinations and delusions exhibit unusually large responses to predictable or unimportant stimuli (Jensen et al., 2008), and smaller responses to important stimuli compared to controls (Murray et al., 2008). Additionally, high-level systems fail to predict and

down-regulate responses to the sensory consequences of patients' own actions or speech (Blakemore et al., 2000; Ford and Mathalon, 2004; Shergill et al., 2005). It therefore seems likely that hallucinations and delusions are linked to abnormal communication and connectivity between high-level and sensory cortex (Mechelli et al., 2007).

An important component of the predictive coding account is inter-area and inter-laminar communication between prediction (feedback) and prediction error (feedforward) systems (Bastos et al., 2012). It is therefore plausible that the laminar distribution of top-down modulations of sensory responses is abnormal in disorders such as schizophrenia, as well as the strength and direction of the modulations themselves. For example, in the Kanizsa visual illusion (Kanizsa, 1976), selective activation of the deep layers of visual cortex, coupled with down-regulation of responses to the shape inducers, is sufficient to induce an illusory visual percept (Kok et al., 2016). In a similar fashion, responses to important external sounds may be suppressed in schizophrenia, and erroneous activation of the deep layers of auditory cortex may induce auditory hallucinations. Future research can utilize laminar fMRI to examine the relative contributions of layers of auditory cortex to responses to externally and internally generated speech in patients with schizophrenia and controls. Such an experiment could offer important further insights into the abnormalities of connections between high-level and sensory cortices in patients who suffer from hallucinations and delusions. Overall, hallucinations and delusions appear to be tightly linked to abnormal connectivity and communication between brain areas (Fletcher and Frith, 2009), meaning laminar fMRI is likely to provide important contributions to our current understanding of the neural mechanisms underlying these symptoms.

11. Challenges and limitations of laminar fMRI

The great excitement about and potential of laminar fMRI is somewhat tempered by several challenges and limitations of the technique, as we will shortly discuss below (also see Uludağ and Blinder, 2017; for a more detailed review). The biggest challenge for laminar fMRI lies in acquiring the spatial specificity to measure and interpret lamina-specific BOLD responses with confidence. BOLD fMRI measures vascular signal changes and its spatial specificity is therefore constrained by the vascular architecture of the brain. Gradient echo (GE) BOLD is particularly susceptible to venous draining artifacts that run orthogonal to the cortical laminae towards the pial surface (Markuerkiaga et al., 2016; Turner, 2002; Uğurbil et al., 2003; Uludağ, Müller-Bierl, & Uğurbil, 2009; Yacoub et al., 2005), resulting in increased signal strength towards the cortical surface (De Martino et al., 2013, 2015; Kok et al., 2016; Koopmans et al., 2011; Muckli et al., 2015; see Fig. 1D). As such the spatial extent of the BOLD response is not necessarily a reliable indicator of the underlying neuronal activity (Poplawsky et al., 2015). The interpretation of laminar fMRI responses can therefore be challenging, particularly if the effect of interest shows a steady increase towards the pial surface.

Several data analysis techniques have been developed to mitigate the effect of draining artifacts on GE-BOLD responses. Koopmans et al. (2010) identified and masked out voxels that overlapped with veins, and were able to identify a peak in the strength of the visual response in layer 4 of human V1 (Fig. 1D). Similarly, Muckli et al. (2015) excluded voxels with larger receptive fields including those believed to be from larger veins. Kok et al. (2016) used a spatial regression approach to decorrelate signals across cortical layers and were successful in detecting an effect specific to deep layers that did not leak into middle or superficial layers (Fig. 1B). In addition, progress has been made towards incorporating blood draining effects across cortical layers in hemodynamic models, which could help to determine the spatial origin of laminar BOLD responses more accurately (Heinzle et al., 2016).

Different methods of data acquisition can also be used to mitigate the effects of venous blood draining on laminar fMRI responses. For example, cerebral blood volume (CBV) based fMRI (Goense et al., 2012; Kim et al., 2013; Poplawsky et al., 2015) and spin echo and 3D GRASE sequences (De

Martino et al., 2013; Muckli et al., 2015; Uludağ et al., 2009) are less susceptible than GE-BOLD to vein artifacts, however they offer less sensitivity than GE-BOLD (Moerel et al., 2017; Yacoub et al., 2005). Moerel et al. (2017) directly compared data acquired from auditory cortex using a GE sequence and 3D GRASE in terms of decoding accuracy and specificity of tonotopic maps. The greater sensitivity of GE-BOLD allowed for better decoding accuracy and larger spatial coverage of tonotopic maps compared to 3D GRASE (though, there was a trend for decoding accuracy to improve towards the pial surface in GE-BOLD data that the authors corrected for with post-processing techniques). In contrast, 3D GRASE was preferable for submillimeter measurements of tonotopy, as there were biases in estimates of frequency preference and selectivity for GE data. It therefore seems that the optimal method of data acquisition depends on the experimental question and types of analyses to be performed. In another example, Huber et al. (2015) were able to improve the relatively low signal-to-noise of CBV-based laminar fMRI by using a higher in-plane resolution than the slice thickness, something which was only feasible because the brain region of interest, the ‘hand-knob’ region of primary motor cortex, has a relatively simple and predictable folding pattern.

Overall, the contribution of venous blood draining effects to the BOLD response makes the interpretation of laminar fMRI data more complicated than standard fMRI studies. However, the above examples provide an array of adjustments that can be made to data acquisition and analysis methods that could be employed depending on the experimental question, brain region of interest and analysis techniques for the study in question. Considering these developments, the current state of laminar fMRI is promising.

12. Conclusions

In conclusion, laminar fMRI provides a method to infer the origin of neural responses, and examine communication between brain areas at a deeper level than previously possible in humans. In this review, we have described some recent successful applications of laminar fMRI that characterized bottom-up and top-down responses in the contexts of visual prediction (Kok et al., 2016; Muckli et al., 2015) and selective attention (De Martino et al., 2015; Scheeringa et al., 2016). We have also outlined other areas of cognitive neuroscience research that stand to gain new insights from laminar fMRI, offering some specific hypotheses from the literature that yield testable predictions for laminar fMRI experiments. We have mostly focused on the consequences of various cognitive functions on responses in primary sensory cortices. However, inter-area and inter-laminar communication is a general principle of human brain function (Friston, 2005; Heeger, 2017), and as such all domains of cognitive neuroscience may benefit from lamina-resolved fMRI. Animal studies have measured laminar responses from other areas such as V4 (Nandy et al., 2017) and temporal regions (Koyano et al., 2016), but at present further research is required to extend the application of laminar fMRI beyond primary cortices. We encourage researchers with the opportunity to embrace this technological development, and anticipate that many advancements in our understanding of human brain function will be gained from measuring lamina-specific fMRI responses.

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References

Albers, A.M., Kok, P., Toni, I., Dijkerman, H.C., De Lange, F.P., 2013. Shared representations for working memory and mental imagery in early visual cortex. *Curr. Biol.* 23 (15), 1427–1431.

Anderson, J.C., Martin, K.A.C., 2009. The synaptic connections between cortical areas V1 and V2 in macaque monkey. *J. Neurosci.* 29 (36), 11283–11293.

Angelucci, A., Levitt, J.B., Walton, E.J.S., Hupe, J.-M., Bullier, J., Lund, J.S., 2002. Circuits for local and global signal integration in primary visual cortex. *J. Neurosci.* 22 (19), 8633–8646.

Azzopardi, P., Cowey, A., 1998. Blindsight and visual awareness. *Conscious. Cogn.* 7 (3), 292–311.

Bastos, A.M., Usrey, W.M., Adams, R.A., Mangun, G.R., Fries, P., Friston, K.J., 2012. Canonical microcircuits for predictive coding. *Neuron* 76 (4), 695–711.

Behrens, T.E.J., Woolrich, M.W., Smith, S.M., Boulby, P.A., Barker, G.J., Sillery, E.L., Matthews, P.M., 2003. Non-invasive mapping of connection between human thalamus and cortex using diffusion imaging. *Nat. Neurosci.* 6 (7), 750–757.

Binzegger, T., Douglas, R.J., Martin, K.A.C., 2004. A quantitative map of the circuit of cat primary visual cortex. *J. Neurosci.* 24 (39), 8441–8453.

Blakemore, S.J., Smith, J., Steel, R., Johnstone, C.E., Frith, C.D., 2000. The perception of self-produced sensory stimuli in patients with auditory hallucinations and passivity experiences: evidence for a breakdown in self-monitoring. *Psychol. Med.* 30 (5), 1131–1139.

Boynton, G.M., 2011. Spikes, BOLD, Attention, and Awareness: a comparison of electrophysiological and fMRI signals in V1. *J. Vis.* 11 (5), 1–16, 12.

Bullier, J., 2001. Integrated model of visual processing. *Brain Res. Brain Res. Rev.* 36 (2–3), 96–107.

Buracas, G.T., Boynton, G.M., 2007. The effect of spatial attention on contrast response functions in human visual cortex. *J. Neurosci.* 27 (1), 93–97.

Carrasco, M., 2011. Visual attention: the past 25 years. *Vis. Res.* 51 (13), 1484–1525.

Cheng, K., Waggoner, R.A., Tanaka, K., 2001. Human ocular dominance columns as revealed by high-field functional magnetic resonance imaging. *Neuron* 32 (2), 359–374.

Corbetta, M., Shulman, G.L., 2002. Control of goal-directed and stimulus-driven attention in the brain. *Nat. Rev. Neurosci.* 3 (3), 215–229.

Crick, F., Koch, C., 1995. Are we aware of neural activity in primary visual cortex? *Nature* 375 (6527), 121–123.

Crick, F., Koch, C., 2003. A framework for consciousness. *Nat. Neurosci.* 6 (2), 119–126.

De Martino, F., Moerel, M., Ugurbil, K., Goebel, R., Yacoub, E., Formisano, E., 2015. Frequency preference and attention effects across cortical depths in the human primary auditory cortex. *Proc. Natl. Acad. Sci.* 112 (52), 16036–16041.

De Martino, F., Zimmermann, J., Muckli, L., Ugurbil, K., Yacoub, E., Goebel, R., 2013. Cortical depth dependent functional responses in humans at 7T: improved specificity with 3D GRASE. *PLoS One* 8 (3), 30–32.

Dumoulin, S.O., Fracasso, A., van der Zwaag, W., Siero, J.C.W., Petridou, N., 2017a. Ultra-high field MRI: advancing systems neuroscience towards mesoscopic human brain function. *NeuroImage*. <http://dx.doi.org/10.1016/j.neuroimage.2017.01.028>.

Dumoulin, S.O., Harvey, B.M., Fracasso, A., Zuiderbaan, W., Luijten, P.R., Wandell, B.A., Petridou, N., 2017b. In vivo evidence of functional and anatomical stripe-based subdivisions in human V2 and V3. *Sci. Rep.* 7 (1), 733.

Felleman, D.J., Van Essen, D.C., 1991. Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex* 1 (1), 1–47.

Fletcher, P.C., Frith, C.D., 2009. Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nat. Rev. Neurosci.* 10 (1), 48–58.

Ford, J.M., Mathalon, D.H., 2004. Electrophysiological evidence of corollary discharge dysfunction in schizophrenia during talking and thinking. *J. Psychiatric Res.* 38 (1), 37–46.

Fracasso, A., Petridou, N., Dumoulin, S.O., 2016. Systematic variation of population receptive field properties across cortical depth in human visual cortex. *NeuroImage* 139, 427–438.

Friston, K., 2005. A theory of cortical responses. *Philos. Trans. R. Soc. Lond. Ser. B, Biol. Sci.* 360 (1456), 815–836.

Gilbert, C.D., Li, W., 2013. Top-down influences on visual processing. *Nat. Rev. Neurosci.* 14 (5), 350–363.

Goense, J., Merkle, H., Logothetis, N.K., 2012. High-resolution fMRI reveals laminar differences in neurovascular coupling between positive and negative BOLD responses. *Neuron* 76 (3), 629–639.

Gouws, A.D., Alvarez, I., Watson, D.M., Uesaki, M., Rodgers, J., Morland, A.B., 2014. On the role of suppression in spatial attention: evidence from negative BOLD in human subcortical and cortical structures. *J. Neurosci.* 34 (31), 10347–10360.

Gutierrez, C., Cola, M.G., Seltzer, B., Cusick, C., 2000. Neurochemical and connective organization of the dorsal pulvinar complex in monkeys. *J. Comp. Neurol.* 419 (1), 61–86.

Harris, K.D., Mrsic-Flogel, T.D., 2013. Cortical connectivity and sensory coding. *Nature* 503 (7474), 51–58.

Harrison, S.A., Tong, F., 2009. Decoding reveals the contents of visual working memory in early visual areas. *Nature* 458 (7238), 632–635.

Haynes, J.-D., Rees, G., 2005. Predicting the orientation of invisible stimuli from activity in human primary visual cortex. *Nat. Neurosci.* 8 (5), 686–691.

Headley, D.B., Weinberger, N.M., 2015. Relational associative learning induces cross-modal plasticity in early visual cortex. *Cereb. Cortex* 25 (5), 1306–1318.

Heeger, D.J., 2017. Theory of cortical function. *Proc. Natl. Acad. Sci.* 201619788.

Heinze, J., Koopmans, P.J., den Ouden, H.E.M., Raman, S., Stephan, K.E., 2016. A hemodynamic model for layered BOLD signals. *NeuroImage* 125 (October), 556–570. <http://dx.doi.org/10.1016/j.neuroimage.2015.10.025>.

Hubel, D.H., Wiesel, T.N., 1972. Laminar and columnar distribution of geniculocortical fibers in the macaque monkey. *J. Comp. Neurol.* 146 (4), 421–450.

Huber, L., Goense, J., Kennerley, A.J., Trampel, R., Guidi, M., Reimer, E., Möller, H.E., 2015. Cortical lamina-dependent blood volume changes in human brain at 7T. *NeuroImage* 107, 23–33.

- Ibrahim, L.A., Mesik, L., Ji, X. ying, Fang, Q., Li, H. fu, Li, Y. Tang, Tao, H.W., 2016. Cross-modality sharpening of visual cortical processing through layer-1-mediated inhibition and disinhibition. *Neuron* 89 (5), 1031–1045.
- Itti, L., Koch, C., 2001. Computational modelling of visual attention. *Nat. Rev. Neurosci.* 2 (3), 194–203.
- Jensen, J., Willeit, M., Zipursky, R.B., Savina, L., Smith, A.J., Menon, M., Kapur, S., 2008. The formation of abnormal associations in schizophrenia: neural and behavioral evidence. *Neuropsychopharmacology* 33 (3), 473–479.
- Kamitani, Y., Tong, F., 2005. Decoding the visual and subjective contents of the human brain. *Nat. Neurosci.* 8 (5), 679–685.
- Kanizsa, G., 1976. Subjective contours. *Sci. Am.* 234 (4), 48–52.
- Kastner, S., Ungerleider, L.G., 2000. Mechanisms of visual attention in the human cortex. *Annu. Rev. Neurosci.* 23, 315–341.
- Kemp, R., Chua, S., McKenna, P., David, A., 1997. Reasoning and delusions. *Reason. Delusions. Br. J. Psychiatry* 170 (5), 398–405.
- Kim, S.-G., Harel, N., Jin, T., Kim, T., Lee, P., Zhao, F., 2013. Cerebral blood volume MRI with intravascular superparamagnetic iron oxide nanoparticles. *NMR Biomed.* 26 (8), 949–962.
- Koch, C., Ullman, S., 1985. Shifts in selective visual attention: towards the underlying neural circuitry. *Hum. Neurobiol.* 4, 219–227 inbook.
- Kok, P., Bains, L.J., van Mourik, T., Norris, D.G., de Lange, F.P., 2016. Selective activation of the deep layers of the human primary visual cortex by top-down feedback. *Curr. Biol.* 26 (3), 371–376.
- Kok, P., De Lange, F.P., 2014. Shape perception simultaneously up- and downregulates neural activity in the primary visual cortex. *Curr. Biol.* 24 (13), 1531–1535.
- Koopmans, P.J., Barth, M., Norris, D.G., 2010. Layer-specific BOLD activation in human V1. *Hum. Brain Mapp.* 31 (9), 1297–1304.
- Koopmans, P.J., Barth, M., Orzada, S., Norris, D.G., 2011. Multi-echo fMRI of the cortical laminae in humans at 7T. *NeuroImage* 56 (3), 1276–1285.
- Koyano, K.W., Takeda, M., Matsui, T., Hirabayashi, T., Ohashi, Y., Miyashita, Y., 2016. Laminar module cascade from layer 5 to 6 implementing cue-to-target conversion for object memory retrieval in the primate temporal cortex. *Neuron* 92 (2), 518–529.
- Lakatos, P., Chen, C.M., O'Connell, M.N., Mills, A., Schroeder, C.E., 2007. Neuronal oscillations and multisensory interaction in primary auditory cortex. *Neuron* 53 (2), 279–292.
- Lamme, V.A.F., Roelfsema, P.R., 2000. The distinct modes of vision offered by feedforward and recurrent processing. *Trends Neurosci.* 23 (11), 571–579.
- Lee, T., Mumford, D., 2003. Hierarchical Bayesian inference in the visual cortex. *J. Opt. Soc. Am. A* 20 (7), 1434–1448.
- Li, Z., 1999. Contextual influences in V1 as a basis for pop out and asymmetry in visual search. *Proc. Natl. Acad. Sci.* 96 (18), 10530–10535.
- Li, Z., 2002. A saliency map in primary visual cortex. *Trends Cogn. Sci.* 6 (1), 9–16.
- Maher, B.A., 1974. Delusional thinking and perceptual disorder. *J. Individ. Psychol.* 30 (1), 98–113.
- Markov, N.T., Kennedy, H., 2013. The importance of being hierarchical. *Curr. Opin. Neurobiol.* 23 (2), 187–194.
- Markuerkiaga, I., Barth, M., Norris, D.G., 2016. A cortical vascular model for examining the specificity of the laminar BOLD signal. *NeuroImage* 132, 491–498.
- Mechelli, A., Allen, P., Amaro, E., Fu, C.H.Y., Williams, S.C.R., Brammer, M.J., McGuire, P.K., 2007. Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. *Hum. Brain Mapp.* 28 (11), 1213–1222.
- Mikellidou, K., Gouws, A.D., Clawson, H., Thompson, P., Morland, A.B., Keefe, B.D., 2016. An orientation dependent size illusion is underpinned by processing in the extrastriate visual area, LO1. *I-Perception* 7 (5), 1–21.
- Moerel, M., De Martino, F., Kemper, V.G., Schmitter, S., Vu, A.T., Ugurbil, K., Yacoub, E., 2017. Sensitivity and specificity considerations for fMRI encoding, decoding, and mapping of voxel preferences at ultra-high field. *NeuroImage*. <http://dx.doi.org/10.1016/j.neuroimage.2017.03.063>.
- Muckli, L., 2010. What are we missing here? Brain imaging evidence for higher cognitive functions in primary visual cortex V1. *Int. J. Imaging Syst. Technol.* 20 (2), 131–139.
- Muckli, L., De Martino, F., Vizioli, L., Petro, L.S., Smith, F.W., Ugurbil, K., Yacoub, E., 2015. Contextual feedback to superficial layers of V1. *Curr. Biol.* 25 (20), 2690–2695.
- Muckli, L., Kohler, A., Kriegeskorte, N., Singer, W., 2005. Primary visual cortex activity along the apparent-motion trace reflects illusory perception. *PLoS Biol.* 3 (8).
- Muckli, L., Petro, L.S., 2013. Network interactions: non-geniculate input to V1. *Curr. Opin. Neurobiol.* 23 (2), 195–201.
- Murray, G.K., Corlett, P.R., Clark, L., Pessiglione, M., Blackwell, A.D., Honey, G., Fletcher, P.C., 2008. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol. Psychiatry* 13 (3), 267–276, 239.
- Murray, S.O., Boyaci, H., Kersten, D., 2006. The representation of perceived angular size in human primary visual cortex. *Nat. Neurosci.* 9 (3), 429–434.
- Nakayama, K., Mackeben, M., 1989. Sustained and transient components of focal visual attention. *Vis. Res.* 29 (II), 1631–1647.
- Nandy, A.S., Nassi, J.J., Reynolds, J.H., 2017. Laminar organization of attentional modulation in macaque visual area V4. *Neuron* 93 (1), 235–246.
- Pasternak, T., Greenlee, M.W., 2005. Working memory in primate sensory systems. *Nat. Rev. Neurosci.* 6 (2), 97–107.
- Petro, L.S., Paton, A.T., Muckli, L., 2017. Contextual modulation of primary visual cortex by auditory signals. *Philos. Trans. R. Soc. B Biol. Sci.* 372, 20160104.
- Phillips, W.A., Larkum, M.E., Harley, C.W., Silverstein, S.M., 2016. The effects of arousal on apical amplification and conscious state. *Neurosci. Conscious.* 2016 (1), niw015.
- Pollen, D.A., 1999. On the neural correlates of visual perception. *Cereb. Cortex* 9 (1), 4–19.
- Poplawsky, A.J., Fukuda, M., Murphy, M., Kim, S.-G., 2015. Layer-specific fMRI responses to excitatory and inhibitory neuronal activities in the olfactory bulb. *J. Neurosci.* 35 (46), 15263–15275.
- Rees, D., Glover, G.H., Liu, J., Wandell, B., 2007. Laminar profiles of functional activity in the human brain. *NeuroImage* 34 (1), 74–84.
- Reynolds, J.H., Heeger, D.J., 2009. The normalization model of attention. *Neuron* 61 (2), 168–185.
- Rockland, K.S., Pandya, D.N., 1979. Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. *Brain Res.* 179 (1), 3–20.
- Rockland, K.S., Virga, A., 1989. Terminal arbors of individual “Feedback” axons projecting from area V2 to V1 in the macaque monkey: a study using immunohistochemistry of anterogradely transported Phaseolus vulgaris-leucoagglutinin. *J. Comp. Neurol.* 285 (1), 54–72.
- Roelfsema, P.R., De Lange, F., 2016. Early visual cortex as a multiscale cognitive blackboard. *Annu. Rev. Vis. Sci.* 2, 131–151.
- Scheeringa, R., Koopmans, P.J., van Mourik, T., Jensen, O., Norris, D.G., 2016. The relationship between oscillatory EEG activity and the laminar-specific BOLD signal. *Proc. Natl. Acad. Sci.* 113 (24), 6761–6766.
- Self, M.W., van Kerkoerle, T., Supér, H., Roelfsema, P.R., 2013. Distinct roles of the cortical layers of area V1 in figure-ground segregation. *Curr. Biol.* 2121–2129.
- Serences, J.T., Ester, E.F., Vogel, E.K., Awh, E., 2009. Stimulus-specific delay activity in human primary visual cortex. *Psychol. Sci.* 20 (2), 207–214.
- Shergill, S.S., Samson, G., Bays, P.M., Frith, C.D., Wolpert, D.M., 2005. Evidence for sensory prediction deficits in schizophrenia. *Am. J. Psychiatry* 162 (12), 2384–2386.
- Shipp, S., 2003. The functional logic of corticostriatal connections. *Philos. Trans. R. Soc. B Biol. Sci.* 358 (1438), 1605–1624.
- Shipp, S., 2004. The brain circuitry of attention. *Trends Cogn. Sci.* 8 (5), 223–230.
- Smith, A.T., Singh, K.D., Greenlee, M.W., 2000. Attentional suppression of activity in the human visual cortex. *Neuroreport* 11 (2), 271–277.
- Stoerig, P., Barth, E., 2001. Low-level phenomenal vision despite unilateral destruction of primary visual cortex. *Conscious. Cogn.* 10, 574–587.
- Stoerig, P., Cowey, A., 1992. Wavelength discrimination in blindsight. *Brain* 115 (2), 425–444.
- Stoerig, P., Cowey, A., 1997. Blindsight in man and monkey. *Brain* 120 (3), 535–559.
- Takahashi, N., Oertner, T.G., Hegemann, P., Larkum, M.E., 2016. Active cortical dendrites modulate perception. *Science* 354 (6319), 1587–1590.
- Tong, F., 2003. Primary visual cortex and visual awareness. *Nat. Rev. Neurosci.* 4 (3), 219–229.
- Tong, F., 2013. Imagery and visual working memory: one and the same? *Trends Cogn. Sci.* 17 (10), 489–490.
- Turner, R., 2002. How much cortex can a vein drain? Downstream dilution of activation-related cerebral blood oxygenation changes. *NeuroImage* 16, 1062–1067.
- Uğurbil, K., Toth, L., Kim, D.S., 2003. How accurate is magnetic resonance imaging of brain function? *Trends Neurosci.* 26 (2), 108–114.
- Uludağ, K., Blinder, P., 2017. Linking brain vascular physiology to hemodynamic response at ultra- high field MRI. *NeuroImage*. <http://dx.doi.org/10.1016/j.neuroimage.2017.02.063>.
- Uludağ, K., Müller-Bierl, B., Uğurbil, K., 2009. An integrative model for neuronal activity-induced signal changes for gradient and spin echo functional imaging. *NeuroImage* 48 (1), 150–165.
- Van Atteveldt, N., Murray, M.M., Thut, G., Schroeder, C.E., 2014. Multisensory integration: flexible use of general operations. *Neuron* 81 (6), 1240–1253.
- Van Kerkoerle, T., Self, M.W., Roelfsema, P.R., 2017. Effects of attention and working memory in the different layers of monkey primary visual cortex. *Nat. Commun.* 8, 1–10.
- Vetter, P., Smith, F.W., Muckli, L., 2014. Decoding sound and imagery content in early visual cortex. *Curr. Biol.* 24 (11), 1256–1262.
- Vroomen, J., de Gelder, B., 2000. Sound enhances visual perception: cross-modal effects of auditory organization on vision. *J. Exp. Psychol. Hum. Percept. Perform.* 26 (5), 1583–1590.
- Watkins, S., Shams, L., Tanaka, S., Haynes, J.D., Rees, G., 2006. Sound alters activity in human V1 in association with illusory visual perception. *NeuroImage* 31 (3), 1247–1256.
- Weiskrantz, L., 1996. Blindsight revisited. *Curr. Opin. Neurobiol.* 6 (2), 215–220.
- Yacoub, E., Harel, N., Ugurbil, K., 2008. High-field fMRI unveils orientation columns in humans. *Proc. Natl. Acad. Sci. U. S. A.* 105 (30), 10607–10612.
- Yacoub, E., Shmuel, A., Logothetis, N., Ugurbil, K., 2007. Robust detection of ocular dominance columns in humans using Hahn Spin Echo BOLD functional MRI at 7 Tesla. *NeuroImage* 37 (4), 1161–1177.
- Yacoub, E., Van De Moortele, P.F., Shmuel, A., Ugurbil, K., 2005. Signal and noise characteristics of Hahn SE and GE BOLD fMRI at 7 T in humans. *NeuroImage* 24 (3), 738–750.
- Yoshor, D., Ghose, G.M., Bosking, W.H., Sun, P., Maunsell, J.H.R., 2007. Spatial attention does not strongly modulate neuronal responses in early human visual cortex. *J. Neurosci.* 27 (48), 13205–13209.
- Zeki, S., 1990. A century of cerebral achromatopsia. *Brain* 113, 1721–1777.
- Zeki, S., 1991. Cerebral akinetopsia (visual motion blindness). A review. *Brain* 114, 811–824.
- Zhang, X., Zhaoqing, L., Zhou, T., Fang, F., 2012. Neural activities in V1 create a bottom-up saliency map. *Neuron* 73 (1), 183–192.