How Layer-Specific fMRI Can Contribute to Understanding Perceptual Disturbances Across Psychiatric Disorders

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Contents

Abstract Perceptual disturbances occur across various sensory domains and contribute to significant suffering in numerous psychiatric and neurological conditions. Despite decades of research into the neural mechanisms underlying these distressing experiences, progress has been relatively limited. Here we explore the potential of layer-specific fMRI to enhance our understanding of these phenomena. We posit that perceptual disturbances can stem from alterations in the neural integration of internally generated signals–such as memory, imagination, prediction, and expectations–with sensory evidence being used to optimize inferences about the world. Emerging evidence suggests that these key computations are distributed across different cortical layers, highlighting the utility of layer-specific imaging in identifying the mechanisms driving such disruptions. We review recent findings that underscore the promise of layer-specific fMRI in elucidating these neural processes and discuss how pharmacological layer-specific fMRI could further advance this understanding. Finally, we address the current limitations of layer-specific fMRI and the progress made toward overcoming these challenges.

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1 Introduction

Perceptual disturbances play an important role in various psychiatric and neurological disorders, including psychosis, autism, anxiety disorders, eating disorders, bipolar disorder, Parkinson's disease and dementia (Berntson and Khalsa 2021; Dakin and Frith 2005; Khalsa et al. 2018; O'Brien et al. 2020; Sterzer et al. 2018). Yet despite the prevalence of these symptoms, their centrality to the illness, and their relation to poor disease outcomes, little is understood about the nature and mechanistic underpinnings of these experiences.

Perceptual disturbances occur across sensory domains, including audition, vision, somatosensation, olfaction, interoception, and proprioception (Eversfield and Orton 2019; Fenelon et al. 2002; Lewandowski et al. 2009; Lim et al. 2016). Within modalities, the types of experiences that can be considered to fall under the term perceptual disturbances are varied as well. Considering just the visual domain, across different disorders, patients might report changes in the appearance of objects, where they might appear unusually bright or intense, or find that objects seem warped, flat, or perceived to look like cardboard cutouts. We might refer to such experiences, where objects are perceived altered, as "illusory." In contrast, full blown hallucinations can also emerge in psychosis or Parkinson's disease, where de novo percepts arise, without a corresponding external stimulus. These hallucinatory experiences range from geometrical patterns, all the way to the experience of fully formed individuals situated in space (Bunney et al. 1999; Dudley et al. 2019). Much theoretical work has attempted to explain these phenomena as deficits in various cognitive or perceptual systems. Some have argued that these disturbances are the result of deficits in attention, reality monitoring, corollary discharge, or the result of an excessive influence of expectations on perception (Ford and Mathalon 2005; McGHIE and Chapman 1961; Powers et al. 2016; Simons et al. 2017; Sterzer et al. 2018).

Changes in interoception–the nervous system's ability to sense internal bodily states–are increasingly implicated in anxiety disorders, eating disorders, and disturbances in the sense of self (Allen et al. 2022; Khalsa et al. 2018; Seth and Tsakiris 2018). In anxiety disorders, heightened interoceptive sensitivity or misinterpretation of bodily signals, such as an elevated heart rate, can amplify fear responses and perpetuate a cycle of hypervigilance (Paulus and Stein 2010). Similarly, in eating disorders, altered interoception can manifest as a disconnect between physiological hunger and satiety cues, contributing to disordered eating behaviors and distorted body image (Khalsa et al. 2015). Moreover, disturbances in interoception may undermine the sense of self, as the ability to integrate bodily sensations with emotional and cognitive processes is central to maintaining a coherent self-concept (Woelk and Garfinkel 2024). These experiences can be construed as perceptual disturbances in and among themselves, where a failure to make proper inferences about one's own bodily states can lead to maladaptive behaviors (Berntson and Khalsa 2021).

As will become clear, there is a good reason to assume that many of these forms of perceptual disturbances can arise from altered information signaling on the level of the cortical microcircuit. Advances in the field of high-field neuroimaging has made it possible to study these microcircuits in a noninvasive way, using a method that has become known as layer-specific fMRI. In this chapter, we introduce the method of layer-specific fMRI and how it can be used to study the neural mechanisms that underlie perceptual disturbances. In order to achieve this, we start by describing a theoretical framework of how laminar mechanisms might underlie perceptual inference. Having such a framework to guide our thinking will be useful, as conceptualizing how perception might go awry requires some understanding of the mechanisms underlying normative perception. We will not attempt to give a comprehensive account of these theories, as insights in how perception is implemented through these mechanisms will likely change over time and are expected to coevolve with how we think of perceptual disturbances. However, we provide enough detail to allow the reader to start thinking about how different layers might give rise to perceptual disturbances. Once this has been covered, we move on to discuss how layer-specific fMRI has been applied in recent years to tackle novel questions in the field of perception and cognitive neuroscience more generally. We consider how comparative studies between clinical and pharmacological groups can start to highlight some of the key mechanisms that underlie these experiences. The field of layer-specific fMRI is new, and it should be noted that at the present moment of writing this review, studies using layer-specific fMRI to study psychiatric or neurological disorders are still sparse. Therefore, our aim is to describe what its potential might be in exploring the neural mechanisms of perceptual disturbance, as well as some of the limitations that still need to be addressed. Central to the discussion here will be its ability to study the diversity of nuanced mechanisms that possibly underlie different psychiatric disorders, in contrast to attempting to reconciling all forms of perceptual disturbances under a single theoretical umbrella.

2 Frameworks to Understand Perceptual Inference

Before comprehending how perception might go awry, we first need a model of normative perceptual inference. Traditionally, perception has been construed as directly reflecting the external world (Gibson 1950). This approach is reflected in neural theories of perception as predominantly a feedforward process, building progressively and sequentially from simple low-level representations (edges and colors) to higher-order cognition like object recognition (Serre et al. 2007). This construes perception as a data-driven, mostly passive process of accumulation of sensory data (see, for example, Marr's computational theory of vision (Marr 2010). In contrast, the constructive approach construes perception as context dependent and

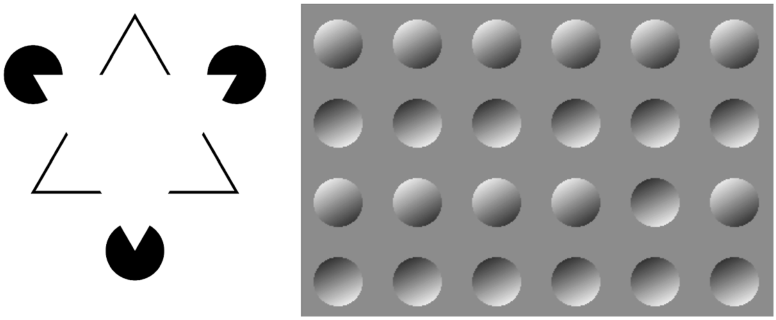


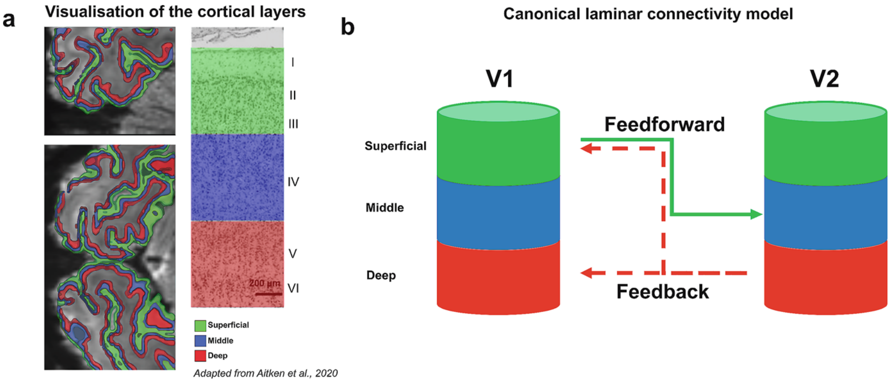
Fig. 1 The constructionist approach suggests that perception is an active process. Examples highlighting the constructionist nature are illusions like the Kanizsa triangle and the convex-concave illusion. Here contextual information leads to perceptual changes, resulting in the perception of illusory contours, or perceiving the same stimulus as concave or convex depending on how lighting is interpreted

active. This view puts a particular importance on top-down influences on perception, most clearly exemplified by visual illusions (Fig. 1) (Gregory 1997; Gregory et al. 1980).

One constructionist view that has become popular is the view that the brain forms a generative model of the world (Clark 2013). Given this assumption, much of cognitive neuroscience has been dedicated to understanding how the brain might form such an internal model in computational terms (Spratling 2017), as well as how such a model might be implemented on a neural level (Bastos et al. 2012, 2020; Friston 2009). Although an extensive discussion of the different theories that are currently popular in the field of cognitive neuroscience is beyond the scope of the current chapter, it is worth highlighting one of these theories, as it helps us understand how perception might go awry in different ways, as well as how layer-specific fMRI might be used to test predictions resulting from them.

Here we use the predictive coding theory to guide the discussion around how layer-specific fMRI can be applied to understanding perceptual disturbances. The benefit of using this theory is that the hypothesized mechanisms that underly perception are believed to be segregated and implemented in different cortical layers (Bastos et al. 2012; Clark 2013; Friston 2009; Spratling 2017). While there are various iterations of this theory that make slightly different claims about the neural mechanisms through which the brain forms a model, there is a common theme among them (see Spratling 2017 for an overview). The general claim in predictive coding theories is that the brain models its environment by making iterative predictions about sensory inputs. These predictions need to somehow be updated by virtue of new sensory evidence to approximate an optimal estimate of the outside world. Most predictive coding theories suggest that this is achieved through the use of a precision-weighted prediction errors, signaling the difference between sensory input and prediction (Bastos et al. 2012). This notion of integrating prior knowledge with new sensory input in a weighted fashion resonates with Bayesian theories of the brain, which suggest that optimal inference requires integrating precision weighted prior knowledge with precision weighted evidence (Friston 2012; Yon and Frith 2021).

How might the brain implement these computational mechanisms? Again, predictive coding theories answer this question in slightly different ways, but we can delineate some commonalities. Many of these theories start from the assumption that the brain is a hierarchically organized system, with feedforward and feedback connections interwoven to form a dense neural network of interconnected systems. Indeed, anatomical work has revealed that in the primate visual cortex, there are many feedforward and feedback connections that seem to make up a hierarchical system (Angelucci et al. 2002; Felleman and Van Essen 1991). Interestingly, they observed a preference for feedback neurons originating from the deep layers (Layers V and VI) of higher-order regions to terminate in the deep and superficial (Layers I, II, and III) layers of the cortex. In contrast, feedforward neurons preferentially originate from the superficial layers and preferentially terminate in the middle layers (Layer IV) of higher-order regions (Fig. 2b). As such, different brain regions form a hierarchical network through layer-specific connections between regions. Notably, the posterior granular insular cortex displays similar laminar differentiation, although the anterior insular cortex lacks a distinguished layer IV (Flynn 1999; Gogolla 2017). Given these anatomical findings, predictive coding theories have suggested there is a functional segregation on the laminar level in the sensory cortex, attributing different functions to different layers (Bastos et al. 2012, 2020; Friston 2018). That is, feedback signals from the deep layers are typically believed to convey predictive information, terminating in the superficial and deep layers of lower



Adapted from Aitken et al., 2020

Fig. 2 (**a**) The superficial, middle, and deep layers can be visualized on a functional EPI scan by dividing the grey matter into three layers with equal volume. Histologically, in the primary visual cortex, the superficial layers capture layers I-III, the middle layer capture layer IV, while the deep layers capture layer V&VI (de Sousa et al. 2010). (**b**) The layers of the early visual cortex have a typical connectivity pattern, where feedforward signals are sent from the superficial layers of lower sensory regions to the middle layers of higher-order regions. In contrast, feedback signals are sent from the deep layers of higher sensory regions to the agranular (deep and superficial) layers of sensory regions sensory regions, explaining away sensory inputs from lower regions. Feedforward sensory input instead arrives in the middle layers, from where it is sent to the nearby superficial layers, and compared to predictive information from higher-order regions. This is then suggested to result in the computation of a prediction error, capturing as yet unexplained sensory input, which is used to update predictions upstream (Bastos et al. 2012; de Lange et al. 2018; Lawrence et al. 2019a; Stephan et al. 2019). While some elements of predictive coding theory are well supported, other aspects await empirical support or refutation. One aspect that has been well supported is that the brain generates predictive signals, about both present and future states (see evidence discussed below). The brain also precision-weights prediction errors during learning (Haarsma et al. 2021). In the sensory domain it is well known that unexpected stimuli can generate stronger cortical responses, but whether these actually represent prediction errors remains unclear (Garrido et al. 2009). Finally, the hierarchical nature of sensory cortices lends them well to hierarchical inference as in predictive coding (see sections below). However, some postulates of predictive coding theory remain less well supported. In particular whether the above-mentioned prediction and error signals are computed by different neural units, as well as the minimization of prediction error through reciprocal exchange between different hierarchical levels, remain less strongly supported (Walsh et al. 2020). However, although the empirical fate of predictive coding theory remains to be decided, it serves as a useful heuristic for the purpose of this chapter in allowing us to frame how layer-specific imaging can be used to further our understanding of how perception can go awry in clinical and neurological disorders.

3 Application of Predictive Coding Theory to Perceptual Disturbances

Although many questions within predictive coding still need to be resolved, this has not prevented clinical researchers from applying it to theorizing how perceptual inference might go awry in clinical disorders like psychosis, autism, anxiety, eating disorders, and neurological disorders like Parkinson's disease and Charles Bonnet Syndrome (Corlett et al. 2019; Khalsa et al. 2018; O'Callaghan et al. 2017; Reichert et al. 2013; Sterzer et al. 2018; Van Boxtel and Lu 2013; Van De Cruys et al. 2014; Zarkali et al. 2019). This is not necessarily a problem. Progress on understanding the neural mechanisms of various pathologies does not require the science on the relevant cognitive mechanisms to be fully settled. One might picture here two rock climbers securing each other's ascent to the top of a mountain. The higher-up climber is in the position to scout the rockface and secure pins, allowing the climber lower-down to follow on more solid footing. The point of this analogy is that a safe ascent of the second climber does not require the top of the mountain to have been reached. Incremental advancement of both climbers is sufficient for successful progress. In concordance with the rise in popularity of normative predictive coding theories of perception and inference, theorists and researchers have applied it to understanding aberrant perceptual inference too. The first of such theories focused on psychosis and emerged almost two decades ago, which suggested that visual and auditory hallucinations could be conceived to be the result of overly strong prior expectations, potentially due to aberrant modulatory neurotransmission, shifting perceptual inference toward priors (Stephan et al. 2006). Indeed, there has been increasing evidence, mostly behavioral, that individuals who report experiencing hallucinations show increased reliance on prior expectations in perception, in the visual and auditory domains (Cassidy et al. 2018; Haarsma et al. 2020; Powers et al. 2017; Schmack et al. 2013; Stuke et al. 2021; Teufel et al. 2015; Zarkali et al. 2019). However, a second strain of studies have complicated this picture somewhat, demonstrating that those who experience psychosis also often display perceptual processing abnormalities that are more in line with a weakened influence on perceptual processing. Findings relating to misinterpreted inner speech (Crapse and Sommer 2008; Feinberg 1978), weaker susceptibility to illusions (Dima et al. 2009, 2010; Haarsma et al. 2020; Pearl et al. 2009; White et al. 2014), and weaker attenuation of sensory consequences in action (Blakemore et al. 2000; Ford and Mathalon 2005; Shergill et al. 2005) might be better understood as instances of weaker priors. Theorists have attempted to resolve this potential contradiction by arguing that the balance between top-down predictive signals and sensory input is shifted in different ways for different symptoms. That is, whereas disturbances in agency might result from diminished predictive signals (Griffin and Fletcher 2017), hallucinations might be the result of overly strong predictive signals (Corlett et al. 2019). Others have suggested that there are subtle differences depending on disease stage or the presence of psychosis in addition to hallucinations (Corlett et al. 2011; Haarsma et al. 2020; Powers et al. 2017; Schmack et al. 2013). Finally, some have suggested that the relative weakening of priors is not specifically correlated with the presence of hallucinations, whereas overly stronger priors are (Corlett et al. 2019; Sterzer et al. 2018).

These contradictions and inconsistencies point to a broader issue, which is that predictive coding theories and Bayesian theories of perception more generally have been difficult to properly constrain, as they tend to be overparameterized. That is, almost any finding can be accounted for by changing some parameter in the theory, and the same finding can often be explained in a multitude of ways, making it difficult to falsify (Haarsma et al. 2022). For example, evidence demonstrating heightened reliance on priors could also be explained by weakened reliance on sensory evidence. These different hypotheses matter, as they might suggest different disease etiologies (see below for a further discussion on this). Layer-specific fMRI could potentially provide some solutions by interrogating more precisely what the role of different feedforward and feedback signals is in perception (Haarsma et al. 2022; Lawrence et al. 2019a; Stephan et al. 2019).

4 Layer-Specific fMRI as a Tool to Study the Computational Architecture of Perception

Much of the development of layer-specific fMRI is a direct result of the wider use of high-field MRI scanners with magnetic field strengths of 7 Tesla and beyond. High-field MRI scanners offer one particular advantage over lower field strengths for layer-specific fMRI studies: the higher magnetic field strengths provide enhanced signal-to-noise ratio (SNR) and therefore allow greater spatial resolution. This allows researchers to distinguish finer structures within the cortex, such as cortical layers and columns, allowing the study of layer-specific activity patterns (Dumoulin et al., 2018; Lawrence et al. 2019b) (Fig. 2a). With the increase in SNR, existing gradient-echo and spin-echo sequences can be optimized to exploit the laminar signal, thereby providing more detailed information about the cortical layers (Han et al. 2019; Norris 2012).

With the advent of high-resolution imaging, the layer-specific fMRI field entered a stage of validation-oriented studies. The primary goal was to compare layer-specific signals to a known gold standard, to build confidence in its utility to reliably measure laminar signals. These studies were therefore not so much focused on revealing novel mechanisms within the human brain but rather on finding concordance between ground truth and results obtained by layer-specific fMRI. Many of the earliest studies were encouraged by finding sensory input primarily modulating the middle layers, both in early monkey work as well as in humans, suggesting that it is possible in principle to differentiate activity in different layers (Chen et al. 2013; Goense and Logothetis 2006; Koopmans et al. 2010, 2011; Polimeni et al. 2010) (Fig. 3a). Subsequent experiments explored the laminar mechanisms underlying more complex processes, e.g., by comparing scrambled and unscrambled figures and stimuli differentially targeting parvo- and magnocellular pathways, revealing differential laminar profiles across these conditions (Olman et al. 2012).

After establishing that layer-specific fMRI can pick up laminar specific signals in the visual cortex, others started to apply it to study more complex perceptual processes. These studies often added to the confidence in the reliability of layer-specific fMRI, as there was considerable overlap with laminar findings from nonhuman animals (Self et al. 2019). Naturally, many studies using layer-specific fMRI are interested in the interplay between feedforward and feedback signaling, and thus many experimental manipulations contrast bottom-up signals and top-down processes such as working memory, imagery, illusory perception, and expectations. Most of these studies have focused on studying the primary visual cortex, as the laminar organization of this area is best understood, and the methods used in the earliest laminar studies were optimized for this region. We therefore discuss work in the visual cortex first.

One of the first studies to explore more complex perceptual processes studied contextual feedback processing in visual scene construction. To test whether specific layers contribute to filling in contextual information, the researchers occluded a quadrant of a visual scene that was previously perceived as a whole (Muckli et al.

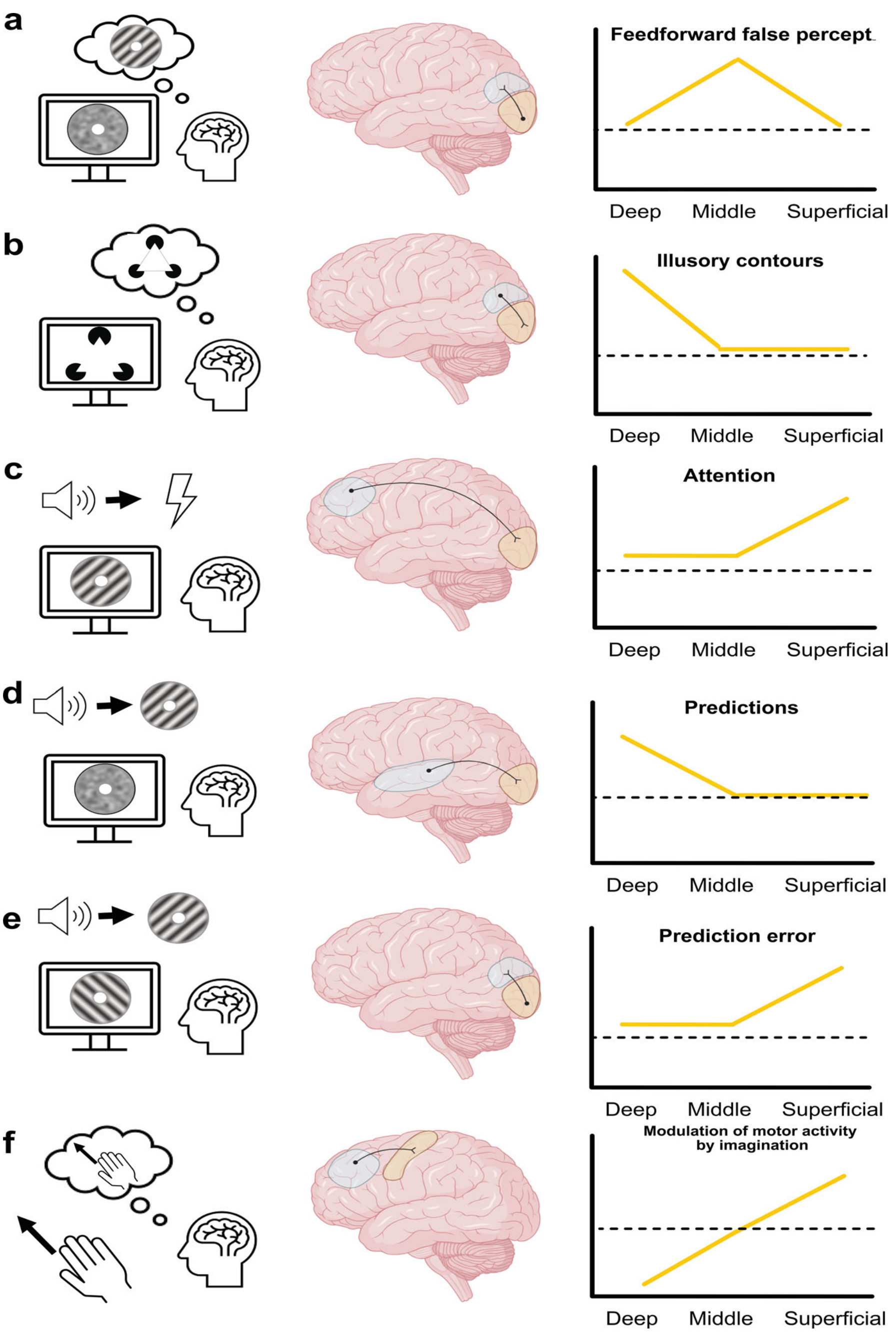


Fig. 3 Layer-specific profiles of different perceptual mechanisms, with a focus on the visual system. Blue regions represent higher-order regions, whereas orange regions represent lower order regions. Connectivity patterns are based on separate studies and were typically not measured in the respective layer fMRI experiments themselves. The laminar profiles reflect the region in which the depicted neural connections terminate. (**a**) The orientation of expected gratings has

2015). Using multivariate techniques, they found that they could decode the scene context from the occluded quadrant specifically from the superficial layers of the visual cortex, suggesting that contextual information is fed back into these layers. A second study focused on the laminar profile of illusory figures induced by the Kanizsa triangle illusion. Using retinotopic mapping, an area of V1 was identified that corresponded to the area in the visual field where the illusory figure was perceived. They found that specifically in conditions where the illusory figure was present, there was heightened activity in the deep layers of V1, in line with nonhuman physiological work (Lee and Nguyen 2001; Pak et al. 2020) (Fig. 3b). Notably, feedback signals do not only exist in the context of low-level visual illusions but extend to higher-order cognitive domains like working memory as well. For example, one study demonstrated that merely maintaining a specific orientated grating in mind was enough to evoke orientation-specific activity in the deep and superficial layers of the primary visual cortex (Lawrence et al. 2018). Again, these findings align nicely with nonhuman animal work, demonstrating similar agranular activity in monkeys performing a working memory task (van Kerkoerle et al. 2017). A second study by the same group reported separate layer-specific modulations of feedback, through feature-based attention, and bottom-up input, with attention most strongly affecting superficial layers, and bottom-up input particularly modulating the middle layers (Lawrence et al. 2019b) (Fig. 3a, c).

The previously discussed studies provide strong evidence that the agranular layers play an important role in a range of top-down perceptual processes, such as contextual processing and working memory. Because much experimental work on the mechanisms underlying hallucinations suggest that they are the result of strongly overweighted expectations about future events, a key question will be whether these expected events are represented in the agranular layers of the early sensory cortex as well. If this is found to be the case, such a mechanism is ideally situated to modulate sensory processing, potentially driving abnormal perceptual experience. Indeed, a series of studies have identified considerable support for the representation of expected events in these layers. One study explored the layer-specific representation of expected sensory templates. Previous studies have shown that merely expecting to see an oriented grating induces a sensory template of that stimulus in the early visual cortex (Kok et al. 2014, 2017). In line with predictive coding theories, subsequent

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Fig. 3 (continued) repeatedly been found to be represented in the deep layers of the visual cortex (Aitken et al. 2020; Haarsma et al. 2023; Thomas et al. 2024). Working memory seems to rely on a combination of the deep and superficial layers (Lawrence et al. 2018). (**b**) False percepts can emerge from activity in the middle layers (Haarsma et al. 2023). The middle layers are also often modulated by bottom-up input (Chen et al. 2013; Goense and Logothetis 2006; Koopmans et al. 2010, 2011; Polimeni et al. 2010; Lawrence et al. 2019b; Yu et al. 2019). (**c**) Low-level perceptual illusions rely on activity in the deep layers (Kok et al. 2017). (**d**) Attention has been shown to modulate the superficial layers (De Martino et al. 2015; Gau et al. 2020; Lawrence et al. 2019b, but see also Klein et al. 2018). (**e**) Prediction errors are represented in the superficial layers (Thomas et al. 2024). (**f**) Imagined movement modulates deep and superficial layers of the motor cortex in opposite directions (Persichetti et al. 2020) work showed that merely expecting a grating on the basis of a visual cue was enough to induce a sensory template specifically in the deep layers of the visual cortex (Aitken et al. 2020) (Fig. 3d). This finding was replicated in a second study where participants had to make judgments about the orientation of a grating embedded in noise, while an auditory cue predicted the most likely orientation. Interestingly, here the deep layers once more represented the expected grating, despite most participants not being aware that the cues predicted the most likely orientation. This suggests that even implicitly the brain can generate sensory templates on the basis of previously conditioned stimuli (Haarsma et al. 2023). In a third study, actions were predictive of upcoming stimuli, with different levels of validity. Once more, only in the valid conditions did the deep layers represent the expected orientation, in line with an important role for these layers in signaling expected stimuli (Thomas et al. 2024). Together, these studies suggest there is converging evidence, at least with regard to simple orientation-like stimuli, that the deep visual cortical layers indeed represent expected stimuli.

Another important claim of predictive coding theories is that there should be different neural populations representing errors and predictions across the cortical hierarchy. This component of predictive coding is one of the less substantiated claims (Walsh et al. 2020). Some indirect evidence in line with this comes from histological work suggesting that feedforward and feedback connections originate from different cell populations (Markov et al. 2014). Electrophysiological work suggests that feedforward and feedback signals are transmitted at different frequencies (Arnal and Giraud 2012; Bastos et al. 2020). More direct evidence comes from studies in mice and monkeys showing that different cell populations in V1 report mismatch and prediction signals (Attinger et al. 2017; Bell et al. 2016; Fiser et al. 2016; Keller et al. 2012; Keller and Mrsic-Flogel 2018; Leinweber et al. 2017), but see also (Muzzu and Saleem 2021) for an alternative view. However, evidence that prediction errors originate from feedforward projecting neurons in the superficial layers has remained sparse (Walsh et al. 2020). A recent layer-specific fMRI study aimed to test this prediction directly (Thomas et al. 2024) (Fig. 3e). Here, the orientation of a grating could either be expected or unexpected following a particular action. When orientations were expected, all layers represented the orientation that was presented. However, unexpected orientations, or prediction errors, were specifically represented in the superficial layers, in line with previous findings from animal work (Bastos et al. 2020).

Layer-specific fMRI has also been used in other sensory modalities, such as the somatosensory domain. For example, one study explored how predictable and unpredictable sensory input preferentially activates different layers in the early somatosensory cortex (S1) and found that like findings in the visual cortex described above, thalamic sensory input preferentially activated the middle layers, whereas predictability mostly modulated the agranular superficial and deep layers (Yu et al. 2019). Another study explored laminar specific signals underlying action. Here, participants were required to tap their fingers while layer-specific activity in the superficial and deep layers in the early motor cortex (M1) was measured. Finger tapping evoked activity in the superficial and deep layers, whereas imagined movements only activated the superficial layers. Further, imagined movement repressed signals in superficial layers but enhanced signals in the deep layers (Persichetti et al. 2020) (Fig. 3f). This further underscores the importance of layer-specific fMRI to distinguish between suppression and sharpening theories of perception (Thomas et al. 2024).

The auditory domain has received considerable attention in layer-specific fMRI studies as well. One study explored frequency preference across layers, as well as its modulation by attention. They found that attention particularly modulated the superficial layers of the primary auditory cortex (De Martino et al. 2015). More recently, the same researchers studied how stimulus complexity is represented across the primary auditory cortex and found that the superficial layers in particular represented more complex features of sounds (Moerel et al. 2019). Studying cross-modal processing and attention, one study found that visual-audio stimuli modulated activity in the deep layers specifically, whereas attention modulated the superficial layers in both primary sensory regions (Gau et al. 2020). Taken together, there is support that just like in the visual cortex, the agranular layers of auditory cortex are primarily involved in feedback processing. Speculatively, content-based feedback signals seem to be represented more often in the deep layers, while attention tends to modulate superficial layers (although note that some have found content in the superficial (Muckli et al. 2015) and attention in deep layers (Klein et al. 2018)). The exact functional roles of the superficial and deep layers remain to be resolved, but their shared role in conveying feedback signals is well established.

Fewer studies have targeted regions outside of the primary sensory regions, creating knowledge gaps waiting to be filled. The insula, with its clear histological differentiation (Flynn 1999; Gogolla 2017), will be a prime future target for layer-specific studies targeted to understand the microcircuits underpinning aberrant interoceptive inference. Further, laminar imaging of higher-order regions like the association cortex will be important in gaining a full understanding of how perceptual disturbances arise, due to the importance of these areas in predictive coding theories. Some have argued that this is now in the realm of possibilities (Finn et al. 2021). One study explored layer-specific responses in the prefrontal cortex during a working memory task, showing heightened activity in the superficial layers during maintenance and deep layers during responses (Finn et al. 2019). Notably, this is in line with work in nonhuman primates (Bastos et al. 2018). A study in word reading demonstrated a particular involvement of the deep layers of the dorsolateral cortex in interpreting words versus pseudowords (Sharoh et al. 2019). Finally, the entorhinal cortex, a crucial interface of the hippocampal complex, has a laminar differentiation in connectivity where superficial and deep layers provide input to and receive output from the hippocampus, respectively (Lavenex and Amaral 2000). Recent laminar studies have demonstrated that it is possible to image the entorhinal layers in a meaningful way (Koster et al. 2018; Maass et al. 2014). This is crucial as the hippocampus is believed to play a critical role in signaling contextual information like perceptual expectations and can play an important role in testing predictive coding theories of hallucinations (Aitken and Kok 2022; Hindy et al. 2016; Kok and Turk-Browne 2018; Schapiro et al. 2012; Stachenfeld et al. 2017; Whittington et al. 2020).

5 Potential Future Avenues in the Study of Perceptual Disturbances

As perception is believed to rely on the interplay of laminar signals integrating across different levels of the cortical hierarchy, perceptual disturbances as seen in various psychiatric and neurological disorders likely have a natural root in these processes. While there have been very few studies that have applied layer-specific fMRI to studying these perceptual disturbances, we can start to speculate how layer-specific fMRI can contribute to understanding them. We will start out with discussing the potential laminar mechanisms that might underlie false inferences in psychosis for two reasons. First, theories considering hallucinations in psychosis have been developed extensively over recent years. Second, the primary modalities affected in psychosis, vision and auditory, have been studied the most using layer fMRI and are therefore the best understood.

As described above, hallucinations as seen in psychosis have been theorized to arise due to increased influences of perceptual expectation signals (Corlett et al. 2019; Powers et al. 2016; Sterzer et al. 2018), which recent studies have reliably linked to signals in the deep layers of the visual cortex (Aitken et al. 2020; Haarsma et al. 2023; Thomas et al. 2024). However, expectations alone are not sufficient to generate perceptual experiences. So how might these expectations give rise to perceptual experiences?

One hypothesis is that it is simply a matter of signal magnitude. If the modulatory drive in the deep layers is strong enough, it might ultimately lead to a concurrent conscious experience. Therefore, what might differentiate these signals from ordinary working memory and expectation signals is that they are simply stronger. Alternatively, it might not so much be the strength of the signal, but rather the level of sensory detail that these feedback signals contain. Indeed, it has been suggested that the brain's ability to separate imagination from reality relies on an inference on this sensory detail. If an experience is vivid and detailed, it is more likely to reflect reality, whereas if an experience is fuzzy and undetailed, it likely reflects imagination, or a different top-down process like expectation or working memory (Dijkstra et al. 2022). This hypothesis could in principle be tested using multivariate techniques in combination with layer fMRI. If this hypothesis is correct, the critical factor in turning a top-down perceptual expectation signal into a hallucinatory perceptual experience is an increased sharpening of the representation of the expected stimulus in the feedback layers of the visual cortex (Abdelhack and Kamitani 2018).

Finally, a third hypothesis may be that hallucinatory experiences arise through modulation of feedforward activity. For example, an expectation of a stimulus might prime pyramidal neurons in the deep cortical layers through receptors on their apical dendrites (Larkum 2013; Spruston 2008). Targeting the apical dendrites would not be expected to drive these pyramidal neurons directly but allow them to function as coincidence detectors (Larkum 2013). In turn, deep layer neurons can modulate incoming sensory input through their projections onto the middle layers (Binzegger

2004; Kim et al. 2014), allowing sensory input concurrent with expectations to be processed more quickly, giving them a head start in signal processing (Antic et al. 2010; Kim et al. 2014; Major et al. 2013). This suggests that a combination of expectations and noisy sensory input is critical in forming hallucinations. What follows from this view is that hallucinations in the absence of such noisy input might be rare. Indeed, this view, where feedback connections modulate sensory inputs rather than having the ability to directly drive activity in the input layers (Kim et al. 2014), may explain why many studies use concurrent noisy input to induce hallucinations (Haarsma et al. 2020; Kafadar et al. 2020; Powers et al. 2017; Schmack et al. 2013, 2021; Stuke et al. 2021; Teufel et al. 2015). That is, if there is no sensory noise to modulate, the feedback signals will not be in the position to give rise to false inferences. In practice, sensory noise could be environmental (e.g., in the dark at night or in the rain) or due to a loss of sensory precision in the early sensory cortex. Indeed, studies have consistently reported decreased sensitivity to sensory input in people with psychosis across various paradigms. For example, schizophrenia patients often show impaired detection of sensory stimuli across different sensory domains (Dondé et al. 2019). This could potentially reflect a separate compounding factor, allowing the hallucinations to manifest. Such a phenomenon is clearly seen in neurological disorders such as Charles Bonnet syndrome, where a loss of sensory input is key in driving the abnormal perceptual experiences (Burke 2002; Ffytche et al. 1998). Recently, behavioral studies have started to show support for this hypothesis in normative nonclinical samples, demonstrating reduced sensitivity to sensory input secondary to heightened hallucinatory reports on stimulus detection tasks (Haarsma et al. 2023; Benrimoh et al. 2024). Layer-specific fMRI could be used to simultaneously study the representation of sensory input and expectation signals and test how the two interact to give rise to hallucinatory experiences.

The hypotheses outlined thus far have pertained mostly to laminar signals in the early sensory cortex, as this is where most of the normative research has been conducted. Ultimately, in order to deepen our understanding of how expectations might shape perception in clinical populations, studies will need to move beyond the sensory cortices. Critical brain regions that are likely key in modulating these effects, and for some of which layer-specific fMRI has been demonstrated to contribute to novel insights, are the hippocampus and medial temporal lobe (Koster et al. 2018; Maass et al. 2014), prefrontal and association cortices (Finn et al. 2019, 2021), cross-modal sensory regions (Gau et al. 2020), and the insula in the case of interoception (Haufler et al. 2022; Nord et al. 2021). All of these regions have been demonstrated to play an integral role in integrating top-down contextual information with sensory signals and might therefore contribute to perceptual disturbances in different ways across clinical conditions (Bar 2007).

While enhanced sensory expectations might underlie some forms of hallucinations, there is significant behavioral evidence that demonstrates a reduced influence of prior expectations in psychosis, typically measured with various auditory and visual illusions, as discussed above. Once more layer-specific fMRI can contribute to our understanding of what underlies these changes in perception. Studies in normative samples that investigated visual and auditory illusions have found a role for agranular layers in mediating these auditory and visual illusions (Gau et al. 2020; Kok et al. 2016). These paradigms could be applied to study the mechanisms that result in the breaking of these illusions in psychosis, i.e., either a weakened influence of feedback signals or an increased reliance on sensory input, thereby outweighing sensory feedback signals.

Predictive coding accounts of hallucinations are not the only theories that could benefit from layer-specific fMRI. A different framework which has been considerably influential in recent years is reality monitoring. This framework rests on the proposal that in order for the mind to keep track of internally and externally generated signals like inner speech and external voices, the brain needs to somehow keep track of which signals are generated internally (Barnes et al. 2003; Bentall et al. 1991; Griffin and Fletcher 2017; Mondino et al. 2019). Central to many of these accounts is the idea that reality monitoring is implemented through comparing sensory experiences to so-called efference copies. These can be conceptualized as predictions of self-generated perceptual experiences, which can modulate sensory processing to give rise to the feeling of agency. Therefore, disturbances in the feeling of agency, as in delusions of control, or attributing inner speech to an external source, could involve aberrant signaling of efference copies or their integration with sensory signals (Griffin and Fletcher 2017). These models could be tested using layer-specific fMRI. Consider recent work that demonstrated laminar specific modulation of somatosensory responses and action signals by predictability and imagined action (Persichetti et al. 2020; Yu et al. 2019). An interesting future avenue of research would be to test whether this extends to the auditory domain and explore whether self-generated speech modulates the agranular layers and whether this is perturbed in individuals with auditory hallucinations. Indeed, layer-specific imaging of speech-sensitive regions has been shown to be feasible (Sharoh et al. 2019). Delusions of agency are also common in psychosis and have been thought to arise from a failure to modulate self-generated sensory signals (Frith 2012). Therefore, another direction of future research could be to explore how agency modulates somatosensory and movement-related signals in S1 and M1, respectively, in psychosis. One might expect that the top-down modulation found in the above-mentioned studies would be diminished in psychosis, providing strong evidence that disturbances in agency arise through diminished top-down modulation of self-generated sensory signals. Further, the posterior insula, a key hub for integrating bodily signals and therefore critical to interoception, has distinct cortical layers (Flynn 1999; Gogolla 2017). The exact function of the different layers remains to be clarified. However, it seems plausible that given the key role that the insula plays in interoception, disturbances in interoception could arise from alterations in how information is integrated on the level of the microcircuit. Indeed, recent studies in schizophrenia demonstrated aberrant cardiac interoception (Ardizzi et al. 2016; Jeganathan et al. 2024; Koreki et al. 2021; Torregrossa et al. 2022), while metacognitive awareness of these disturbances seems intact (Torregrossa et al. 2022). Interestingly, these disturbances seem to correlate with positive symptoms (Ardizzi et al. 2016; Koreki et al. 2021, although not in Jeganathan et al. 2024).

Given the importance of the insula in interoception (Fermin et al. 2022; Hassanpour et al. 2018; Nord et al. 2021; Simmons et al. 2013; Vicario et al. 2020), it is likely that such disturbances in psychotic disorders like schizophrenia find their origin in dysfunctional information processing on the level of the insular microcircuit.

Thus, the emergence of layer-specific fMRI provides a great opportunity to explore how perception might go awry across multiple sensory domains and clinical disorders, promising to shine a new light on unanswered questions.

6 Pharmacological Layer-Specific fMRI

Predictive coding theories of perception attribute important roles to various neurotransmitter systems in mediating the balance between feedback and feedforward signaling (Sterzer et al. 2018). If changes occur in these neuromodulatory systems, this balance can become perturbed, leading to false inferences in a myriad of ways. Imaging the laminar mechanisms that underlie perception while participants undergo different drug challenges could therefore provide invaluable insights into the different ways perception might go awry in clinical disorders. By characterizing how different signals can become perturbed and comparing these changes to what is observed in a disorder, we can start to see the similarities and differences between the clinical and pharmacological theories that are aimed at capturing the same phenomena. For instance, such studies might show that while psychosis patients and individuals undergoing a dopamine challenge might both increase their rates of false alarms on a detection task, the laminar mechanisms through which these behavioral reports manifest might be different. Thus, comparative pharmacological and clinical layer-specific imaging studies will be key in ultimately understanding these disorders. Here we review several possible novel directions of research.

One neurotransmitter system that has long been linked to the etiology of schizophrenia is the NMDA-receptor. The NMDA-receptor theory of schizophrenia goes back a number of decades (Olney et al. 1999) but has gained increasing support through various lines of genetic, molecular, and immunological evidence that suggest an important role for the glutamate system and the NMDA-receptor specifically in modulating some of the symptoms of schizophrenia (Lennox et al. 2017; Merritt and Egerton 2017; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Neuroimaging studies have demonstrated that NMDA-receptor agonists like ketamine perturb error signaling in associative learning paradigms (Corlett et al. 2006, 2016), as well as in mismatch negativity paradigms (Weber et al. 2020). Given the prevalence of NMDA-receptors on pyramidal feedback cells (Fox et al. 1989; Rosier et al. 1993), a plausible hypothesis would be that these perturbations in learning and sensory processing arise due to interference with feedback signaling. Indeed, there is some work in humans that shows that ketamine interferes with feedback signaling (van Loon et al. 2016). Alternatively, the described experimental effects could be explained by enhanced feedforward signaling. Here, layer-specific fMRI could be used to distinguish between these two competing hypotheses by investigating whether NMDA-antagonists interfere specifically with signaling in the deep layers or whether they alternatively enhance feedforward signaling by modulating the middle layers.

While the NMDA-receptor has mostly been associated with feedback signals, the cholinergic system has often been associated with modulating feedforward precision (Moran et al. 2013; Stephan et al. 2006). The cholinergic system might play an important part in the etiology of schizophrenia. For example, there are studies suggesting a loss of sensory precision in schizophrenia due to reduced cholinergic tone (Higley and Picciotto 2014). Further, in neurological conditions like Alzheimer's disease, Lewy-body dementia, and Parkinson's disease, reduced cholinergic function has been consistently related to an increase in visual hallucinations (O'Brien et al. 2020). Experimental evidence using an acetylcholine agonist has been shown to induce hallucinations by sensory conditioning (Warburton et al. 1985), suggesting a mechanistic role for cholinergic disturbances in hallucinations. Again, layer-specific imaging could be used to study whether cholinergic modulation primarily affects feedforward signaling through modulations of the middle and perhaps superficial layers or whether it perturbs feedback signaling in the deep layers instead.

The serotonin system, particularly the 5HT2a receptor that is modulated by classical psychedelics, is another promising neurotransmitter system that is likely to play a role in perceptual disturbances. Although research linking hallucinations in schizophrenia to the serotonin system is somewhat limited, there is increasing evidence that in Parkinson's disease it is a key contributor to visual hallucinations. Previous research has linked 5HT2a receptors in the visual ventral system to the prevalence of visual hallucinations in Parkinson's disease (Ballanger et al. 2010; Huot et al. 2010). Moreover, Pimavanserin, a partial 5HT2a agonist, has shown promising results in treating visual hallucinations in Parkinson's disease (Cummings et al. 2014; O'Brien et al. 2020). The exact mechanisms through which the 5HT2a serotonin system perturbs perceptual processing remain unclear. Some have argued that 5HT2a agonists weaken the influence of prior beliefs (Carhart-Harris and Friston 2019). Indeed, there is some indirect evidence for this. For example, some sensory processing phenomena believed to rely on feedback processing are reduced under psychedelics, like mismatch negativity responses (Timmermann et al. 2018), and the experience of illusory contours (Kometer et al. 2011, 2013), and binocular rivalry is altered as well (Carter et al. 2005, 2007). Neurophysiological studies have demonstrated that these substances alter glutamatergic signaling in layer V neurons, which, given their role in feedback processing, gives credence to the altered feedback processing hypothesis (Aghajanian and Marek 1999). However, the complex hallucinations that are sometimes experienced under these substances seem less compatible with the weaker prior account. Here, laminar imaging can help elucidate this apparent contradiction and test directly whether deep layer signaling of visual illusions (Kok et al. 2016) is perturbed by administration of psychedelics, whereas perhaps more cognitive expectation signals in the deep layers (Aitken et al. 2020; Haarsma et al. 2023) are enhanced. The origin of the top-down drive in these two instances could be different, with the former originating from higher regions within the visual cortex (Pak et al. 2020), and the latter from the hippocampus (Aitken and Kok 2022).

Finally, dopamine has long been implicated in the etiology of psychosis, both in schizophrenia and Parkinson's disease (Howes and Kapur 2009; Meltzer and Stahl 1976). Given the lack of dopamine receptors in the sensory cortex, it is unlikely that dopamine directly affects early sensory processing. Instead, what dopamine might do is enhance the influence of higher-order beliefs on lower-level sensory processing. Indeed, recent evidence from animal studies has suggested that dopamine might do exactly this (Schmack et al. 2021). In a series of experiments, it was demonstrated that hallucination-like behavior was preceded and causally affected by dopamine levels in the caudate nucleus. One hypothesis might be that activity in the caudate enhances feedback signals in the deep layers of the early auditory cortex, which could be studied using laminar imaging. Such evidence would strongly substantiate a role for dopamine in enhancing sensory prediction signals.

Thus, the combination of pharmacological and clinical layer-specific fMRI studies could provide key insights into the various ways perception can go awry. Comparative approaches are particularly encouraged here, as the same behavioral phenomenon might arise through different mechanisms, which layer-specific fMRI could help uncover.

7 Relevance of Layer-Specific fMRI to Precision Medicine

In addition to layer-specific fMRI's potential to test different hypotheses about what underlies perceptual aberrancies in illnesses like psychosis or Parkinson's disease, one of the more exciting prospects is that it allows taking a personalized approach to understanding these mechanisms. There are a range of theoretical papers that have been rightfully influential in how we currently understand hallucinations. However, a potential drawback of such theoretical accounts is that there is often an underlying assumption that there is a single explanation that underlies the broad category of hallucinatory phenomena. While this may be true to some extent, perhaps in the sense that there is a final common pathway that underlies all conscious experience, there is a potential risk that this approach loses sight of the various ways that perception can go awry. Perhaps an alternative approach might be to start with a theoretical framework in which to understand perception and use this to specify the diversity of mechanisms through which perception can go awry. This type of approach, which we have taken in this chapter, can provide a roadmap toward understanding hallucinations that releases us from the obligation to find a single explanation that subsumes all hallucinatory phenomena. A major advantage is that it instead allows us to think about the various routes that may lead to hallucinations, something that may be valuable for explaining individual variations across and even within conditions. Taking such an approach, auditory hallucinations as seen in schizophrenia need not arise through the same mechanisms as hallucinations seen in Parkinson's disease. In psychosis, the types of experiences that are typically considered to be hallucinations can range from low-level perceptual disturbances, such as geometrical patterns, to high-level hallucinations such as seeing fully formed entities or hearing voices, referred to as minor and major phenomena respectively (Mocellin et al. 2006; Pagonabarraga et al. 2016). Given their differences in phenomenology, these might well arise from different mechanisms, and methods like layer-specific fMRI could allow for a more nuanced understanding of these mechanisms.

Embracing this view could allow for a more personalized approach in which future layer-specific imaging studies could play a role. For example, in a recent study, participants occasionally reported perceiving oriented gratings that were not actually presented, with high levels of confidence. In this instance, false percepts were not driven by cued expectations and were reflected in the middle input layers of the visual cortex, potentially reflecting a form of feedforward hallucinations (Haarsma et al. 2023). Expectation-driven hallucinations, on the other hand, are more likely to result from deep layer signals (Aitken et al. 2020; Haarsma et al. 2023; Thomas et al. 2024). Therefore, in future, layer-specific fMRI could be used as a tool to identify patients' unique mechanistic profiles, allowing us to potentially tailor treatment accordingly.

As discussed in the previous section, extending layer-specific fMRI to include pharmacology will be key in this endeavor, and can aid our understanding of the different ways perception can go wrong. For example, false inferences during perceptual discrimination tasks might be the result of excessive feedforward signaling in some patients, whereas they result from enhanced feedback signals in others. If neuromodulatory systems are primarily involved in feedback over feedforward mechanisms, and vice versa, these systems could then be future targets of intervention depending on whether a given patient presents a feedforward or feedback layer profile during false inferences. Thus, although it is still likely a long way off, in theory laminar imaging has the potential to identify personalized treatment targets.

8 Challenges

As layer-specific fMRI is still a relatively novel method, there are still several challenges that limit its application in clinical groups, and overcoming these challenges will likely increase its potential impact. One well-known issue is that large draining veins in the cortex cause a bias towards the superficial layers, as BOLD signal arising from neural activity in deeper layers flows upward to the pial surface (Uludağ and Blinder 2018). This phenomenon complicates interpretation of conventional BOLD-based methods (Kay et al. 2019). The earliest studies attempted to identify voxels containing veins, which was reasonably successful in removing some bias (Koopmans et al. 2010). Alternatively, using non-BOLD-based fMRI sequences could address the root cause of the problem (Huber et al. 2019). One such method is CBV-weighed VASO (Lu et al. 2003), which has been demonstrated to have more local specificity and a more equally weighted contrast across the different cortical depths. However, the overall sensitivity of the obtained signals is reduced compared to more conventional Gradient Echo (GE) EPI sequences (Huber et al. 2015).

Another issue relates to restricted brain coverage, which limits layer-specific fMRI's ability to study whole-brain laminar dynamics. Although SS-SI-VASO or MAGEC_VASO sequences seem to provide superior brain coverage over conventional methods while not relying on the BOLD response for their signals (Huber et al. 2019). Given the importance of achieving high spatial resolution, motion artefacts can be another confounding factor, which might be particularly pertinent for older populations that struggle to lie still for the long periods of time layer-specific imaging requires. Prospective motion correction can limit the amount of pre-processing required once the data has been acquired (Bause et al. 2020). Further, developments in hardware to make participants more comfortable help to reduce motion.

Geometric distortions commonly occur in echo planar imaging (EPI) fMRI sequences. Worryingly these issues are exacerbated at higher magnetic field strengths, as the inhomogeneities in the b0 field become exacerbated, limiting the spatial selectivity of the fMRI signal. This is a considerable problem for layer-specific fMRI, which naturally requires high spatial selectivity. These issues can be partially corrected by acquiring reversed encoding images, which allow the researcher to measure the degree of distortion and adjust for them. Indeed, recently this method has been shown to work well for 3D-epi sequences, where the distortions were corrected in the areas where they typically occur the strongest, i.e., the frontal and temporal areas of the brain. Given the amount of distortions in these areas at higher field strengths, deploying distortion correction will be particularly pertinent when layer-specific imaging will move from the early sensory regions toward higher-order regions like the association and frontal cortices (Malekian et al. 2023).

Currently, layer-specific imaging studies most commonly achieve a voxel-resolution of 0.8 mm isotropic, which is sufficient to separate activity into three separate layers within the visual cortex, as the typical thickness of the grey matter is 2.5–3 mm on average. This means that activity in various neighboring laminae, such as layers V and VI, will be averaged together, limiting the extent to which we can make inferences about the contribution of different layers to perception. Preliminary work has achieved higher resolution images (0.2 mm) by using a line-scanning method (Morgan et al. 2020). If this was to become the standard, further delineation of the contribution of different laminae might come within reach.

A well-known limitation of fMRI is that it suffers from poor temporal resolution, which, given the importance of the timing of various neural events to theories of perception, limits its potential. Some potentially promising, but preliminary, work in anesthetized mice has been reported to be able to overcome the temporal limitation of fMRI by adopting a novel sequence referred to as DIANA (short for Direct Imaging of Neuronal Activity) (Toi et al. 2021). Using this sequence, the researchers were able to obtain laminar-specific neural (rather than hemodynamic) signals from the mouse somatosensory cortex with very high temporal resolution. However, some recent replication attempts have failed so far; thus its application in humans is still far from certain (Choi et al. 2023; Hodono et al. 2023).

To complement layer-specific fMRI, other avenues of noninvasive imaging could be explored. In recent years laminar MEG has emerged as a potentially exciting tool to study perception and cognition. Due to its ability to measure fluctuations in the magnetic field that are a direct consequence of electrical neural signals, it reflects a more direct measure of neural activity and is thereby only constrained by the quality of the data and the models used to make inferences about it (Bonaiuto et al. 2018a, b; Liuzzi et al. 2017; Meyer et al. 2017; Troebinger et al. 2014a, b).

Finally, in order to properly interpret layer-specific fMRI results, one needs to make a reliable assessment of the distribution of the histological layers across cortical depth. While the distribution of layers in the early sensory regions is fairly stable, in higher-order regions like the association cortex, the distribution of layers across depths is more variable (Finn et al. 2021). However, progress can be made by using evidence from anatomical images to gain information about the laminar distribution in higher-order regions like the association cortex. These include diffusion MRI, T1-weighted imaging of the myeloarchitecture, and magnetic susceptibility imaging, as well as using information from whole-brain laminar atlases, which will allow for more accurate estimations of the distribution of layers across cortical depth (Callaghan et al. 2014; Dinse et al. 2015; Finn et al. 2021; Trampel et al. 2019; Wagstyl et al. 2020).

9 Conclusion

Layer-specific fMRI holds great potential for drilling down on some of the leading theories of how perceptual disturbances emerge across various clinical and neurological disorders. By combining it with pharmacological theories of perception, we can start to see the similarities and divergences in how perception can go awry. Ultimately, these methods could aid in developing personalized treatments, helping to alleviate the suffering resulting from perceptual disturbances more effectively.

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