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Auditory processing control by the medial prefrontal cortex: A review of the rodent functional organisation

A Hockley [a,b,c,*], MS Malmierca [a,b,c,1]

[a] Cognitive and Auditory Neuroscience Laboratory, Institute of Neuroscience of Castilla y León, University of Salamanca, Salamanca, Spain
[b] Department of Cell Biology and Pathology, University of Salamanca, Salamanca, Spain
[c] Institute for Biomedical Research of Salamanca, Salamanca, Spain

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ABSTRACT

Afferent inputs from the cochlea transmit auditory information to the central nervous system, where information is processed and passed up the hierarchy, ending in the auditory cortex. Through these brain pathways, spectral and temporal features of sounds are processed and sent to the cortex for perception. There are also many mechanisms in place for modulation of these inputs, with a major source of modulation being based in the medial prefrontal cortex (mPFC). Neurons of the rodent mPFC receive input from the auditory cortex and other regions such as thalamus, hippocampus and basal forebrain, allowing them to encode high-order information about sounds such as context, predictability and valence. The mPFC then exerts control over auditory perception via top-down modulation of the central auditory pathway, altering perception of and responses to sounds. The result is a higher-order control of auditory processing that produces such characteristics as deviance detection, attention, avoidance and fear conditioning. This review summarises connections between mPFC and the primary auditory pathway, responses of mPFC neurons to auditory stimuli, how mPFC outputs shape the perception of sounds, and how changes to these systems during hearing loss and tinnitus may contribute to these conditions.

1. Introduction

There is increasing interest on the function of the medial prefrontal cortex (mPFC) in relation to auditory processing, as it has the capability to control perception via top-down modulation of the central auditory pathway (Hamm et al., 2021; Sun et al., 2022). Located in the frontal lobe, the mPFC is a brain area responsible for many higher-order processes including attention, decision-making, learning, memory and emotion. Recent work has demonstrated mPFC responds to context of auditory stimuli, such as deviant stimuli or reward detection (Casado-Román et al., 2020; Zhao et al., 2019). Furthermore, advances in experimental techniques now allow neural recordings from awake rodents undertaking behavioural tasks where auditory modulation from the prefrontal cortex may be most relevant.

Auditory functions of the human PFC (NB: not specific to rodent mPFC) also have potential clinical implications. Disrupted neurodevelopment and dysfunction of the PFC is implicated in many neuropsychiatric diseases such as schizophrenia, anxiety, attention deficit hyperactivity disorder, post-traumatic stress disorder and bipolar disorder (Chini and Hanganu-Opatz, 2021; Kenwood et al., 2022). Schizophrenia can be associated with auditory symptoms such as hallucinations, which appear to be due to prediction deficits (Bansal et al., 2018; Shergill et al., 2005). Thus, understanding how PFC controls auditory perception has great translational potential.

We review anatomy of the rodent mPFC in comparison to the primate, inputs to and outputs from the primary central auditory pathway, responses of mPFC neurons to auditory stimuli, and how processing of higher-level information in the mPFC can shape the perception of sounds and behavioural responses to auditory stimuli.

2. Defining rodent mPFC

Mammals such as rodents and primates share similar brain organization, but due to differences in evolution surrounding executive function ability, the structure of mPFC has diverged. Agranular areas of the mPFC are shared across mammalian species, however the nomenclature for prefrontal areas differs between rodents and primates. The rodent mPFC is formed of 4 main areas: anterior cingulate cortex (ACC; area

* Corresponding author.
E-mail address: adamhockley@usal.es (A. Hockley).
[1] Co-corresponding author.

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24), prelimbic cortex (PL; area 32), infralimbic cortex (IL; area 25) and secondary motor cortex (M2) (Seamans et al., 2008; Uylings et al., 2003). There is debate over whether M2 can be considered a true part of the rodent prefrontal cortex, as is has projections to jaw and tongue muscles (Yoshida et al., 2009) and electrical stimulation produces movements of head and neck muscles (Brecht et al., 2004; Erlich et al., 2011). In a survey of 38 prefrontal researchers, ~25 % considered M2 to be a part of rodent prefrontal cortex (Laubach et al., 2018), therefore, for the sake of completeness we will also review data that exists from the M2, despite it not being a true 'prefrontal' area.

By comparison, the primate ACC refers to a combination of areas 24, 25, and 32, which historically has created issues in translation of research between fields (see Laubach et al., 2018). Further, the primate prefrontal cortex also includes granular, isocortical areas not present in other mammals (Preuss and Wise, 2022). Despite these nomenclature issues, the rodent mPFC is homologous of the ACC of primates and has many of the same structural and functional characteristics, which are functionally divided in mPFC subregions albeit without such distinct differentiation as primate PFC (Brown and Bowman, 2002). The applicability of translating PFC research across species is debated, and therefore this review will focus largely on research of auditory functions of rodent mPFC, which could therefore be pertinent to auditory functions of ACC in primates.

3. Anatomy & auditory connections of mPFC

The rat mPFC is composed of 4 major areas: ACC, PL, IL and M2 (Gabbott et al., 1997; Laubach et al., 2018; Vogt and Paxinos, 2014). These areas possess different inputs and projection patterns, making them anatomically and functionally distinct, however not all studies differentiate between the subregions, instead preferring to study the mPFC as a whole. When possible, in this review we will compare and contrast subregions, but with the current research this is not always possible.

4. Inputs to mPFC

Auditory inputs to the rodent mPFC have been shown but appear to be somewhat limited (Fig. 1). For example, an early study used retrograde tracer injected into the rodent mPFC and showed labelled cells in auditory cortex (AC). However, no mPFC labelling was observed when anterograde tracers were injected into the AC (van Eden et al., 1992). These divergent results may be due to the limitation of using conventional tracers available at the time. A more recent study using modern viral tracers has mapped all cortical inputs to the mPFC in rodents and showed inputs from almost the entire isocortex, where inputs from the primary motor and somatosensory areas are much stronger than those from auditory areas (Ährlund-Richter et al., 2019). One optogenetic study also provides evidence for an AC-mPFC projection, specifically to the PL subregion (Concina et al., 2018). Moving ventrally, from ACC-PL-IL there is a shift from primarily sensory inputs to greater limbic inputs (Hoover and Vertes, 2007), suggesting that AC inputs are likely concentrated to the ACC. The mPFC also receives broad input from the thalamus (Xue et al., 2022), but the extent to which inputs may arise from the medial geniculate body is unclear. In contrast, auditory inputs in primates arise from the superior temporal gyrus and largely innervate the lateral prefrontal cortex (reviewed by Plakke and Romanski, 2014; Romanski and Averbeck, 2009). These inputs to lateral PFC areas are likely transmitting higher-order auditory information of complex auditory stimuli, resulting in PFC activation in response to stimuli contexts (Plakke et al., 2013). In summary, it appears that despite not being an auditory brain area by the classical definition, mPFC receives direct input from the ascending auditory pathway, which is likely more concentrated to the ACC.

The mPFC also receives strong direct inputs from non-auditory brain areas (Fig. 1). For example, there is a strong connection from the hippocampus, which likely allows transmission of information on how the current context relates to past experiences (reviewed by Alexander et al., 2019). In the rodent, these direct hippocampal projections are excitatory and concentrated to the PL and IL regions (Jay et al., 1992; Jay and Witter, 1991; Liu and Carter, 2018; Verwer et al., 1997). Direct cholinergic inputs to the mPFC from the basal forebrain also exist and are thought to convey arousal, attention, and learning (Bloem et al., 2014; Sun et al., 2019). Based on these inputs, it is clear that the mPFC is not a sensory cortex per se, and instead acts as a processor of higher-order information such as context, learning, attention and decision-making.

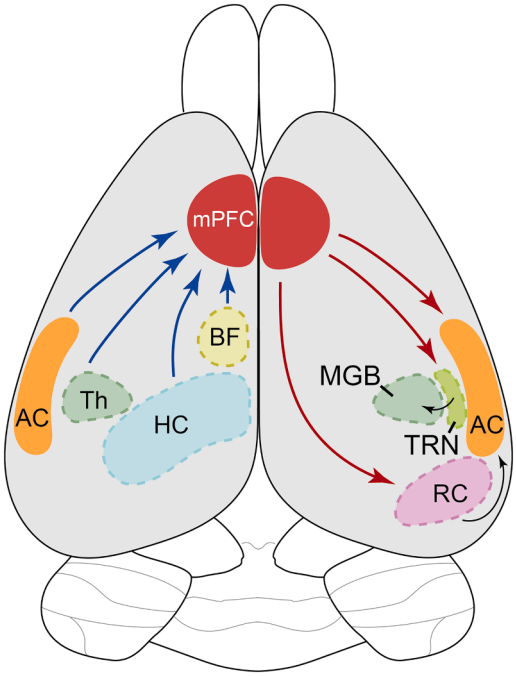

Fig. 1. A schematic diagram of direct inputs to rodent mPFC (left; blue), and auditory-related outputs (right; direct red, indirect black). Note that ascending and descending inputs are shown in the left- and right hemisphere separately for simplicity. For the sake of clarity, only inputs to mPFC thought to be most important for auditory processing control have been included, and other isocortex inputs from somatosensory and motor areas have been omitted. Dark coloured brain areas are on the dorsal surface, whereas lighter shaded areas with dashed outline are more located ventrally. AC auditory cortex; mPFC medial prefrontal cortex; BF basal forebrain; HC hippocampus; Th thalamus; RC rhinal cortex; MGB medial geniculate body; TRN thalamic reticular nucleus.

4.1. mPFC outputs to auditory areas

In order to implement the wide variety of higher-order cognitive functions based in the rodent mPFC, there are a great diversity of outputs to areas such as amygdala, striatum, claustrum, thalamus, ipsilateral striatum, pons and periaqueductal grey (reviewed by Anastasiades and Carter, 2021). While these likely have many effects on perception, here we summarise the direct or indirect outputs to the primary auditory pathway, as these are likely the most important for modulation of auditory processing.

The mPFC is thought to convey higher-order information to sensory cortices in a top-down manner. mPFC connections are capable of modulating sensory cortices with excitation or inhibition, so the function of these direct connections is unclear without functional studies (Schneider et al., 2014; Zhang et al., 2014). In mice, retrograde tracer injections to AC have shown projections from the anterior part of the ACC, with limited projections from PL and IL (Sun et al., 2022). Labelling of neurons in the anterior part of the ACC also produced expression

in the auditory cortex, whereas injections into the posterior ACC largely labelled projections to the visual cortex, suggesting that the anterior-mPFC is more auditory-focussed (Sun et al., 2022). Two distinct groups of neurons in the anterior ACC project to AC (from deep layers) and lateral rhinal cortex (from superficial and deep layers). The lateral rhinal cortex neurons then also project to AC, resulting in a direct and indirect pathway from AAC-AC (Liang et al., 2023). A recent preprint has also mapped the ACC-AC pathway using anterograde and retrograde optogenetic virus expression (Anbuhl et al., 2023). The outputs of mPFC to visual cortex are capable of birectionally modulating activity dependent on context (Hamm et al., 2021), however the mPFC-AC function is less well understood and further studies are needed to understand these outputs.

While the mPFC does not project directly to the medial geniculate body (MGB), there exist direct and indirect (via the basal forebrain) projections to the thalamic reticular nucleus (TRN; Nakajima et al., 2019; Zikopoulos and Barbas, 2006). The TRN is capable of altering MGB activity through inhibitory TRN-MGB projections, thus completing the indirect mPFC-MGB pathway (Barry et al., 2017; Yu et al., 2009). This inhibition of MGB neurons allows filtering of sensory stimuli, specifically by suppressing the distracting sensory modality and suppression of background noise (Nakajima et al., 2019). This demonstrates a pathway for sensory attention based on decision-making processes in the mPFC and explains how the mPFC may implement higher-order cognitive functions in a top-down manner.

5. Auditory responses in mPFC

As a result of strong afferent input from the cochlea, neurons in the lemniscal central auditory pathway generally respond to tones and are usually most responsive to a specific frequency (Carbajal and Malmierca, 2018). In comparison, when tones of varied frequencies and intensities are presented randomly, mPFC neurons do not alter spike rates (Fig. 2; Casado-Román et al., 2020). Studies have shown that mPFC neurons respond during more complex trains of auditory stimuli, demonstrating that mPFC is not coding spectral properties and instead is fundamentally driven by the contextual characteristics of auditory stimulation, such as prediction error or reward detection (Casado-Román et al., 2020; Zhao et al., 2019). The functions of mPFC therefore likely depend on the stimuli presented, and these potential auditory functions are discussed below.

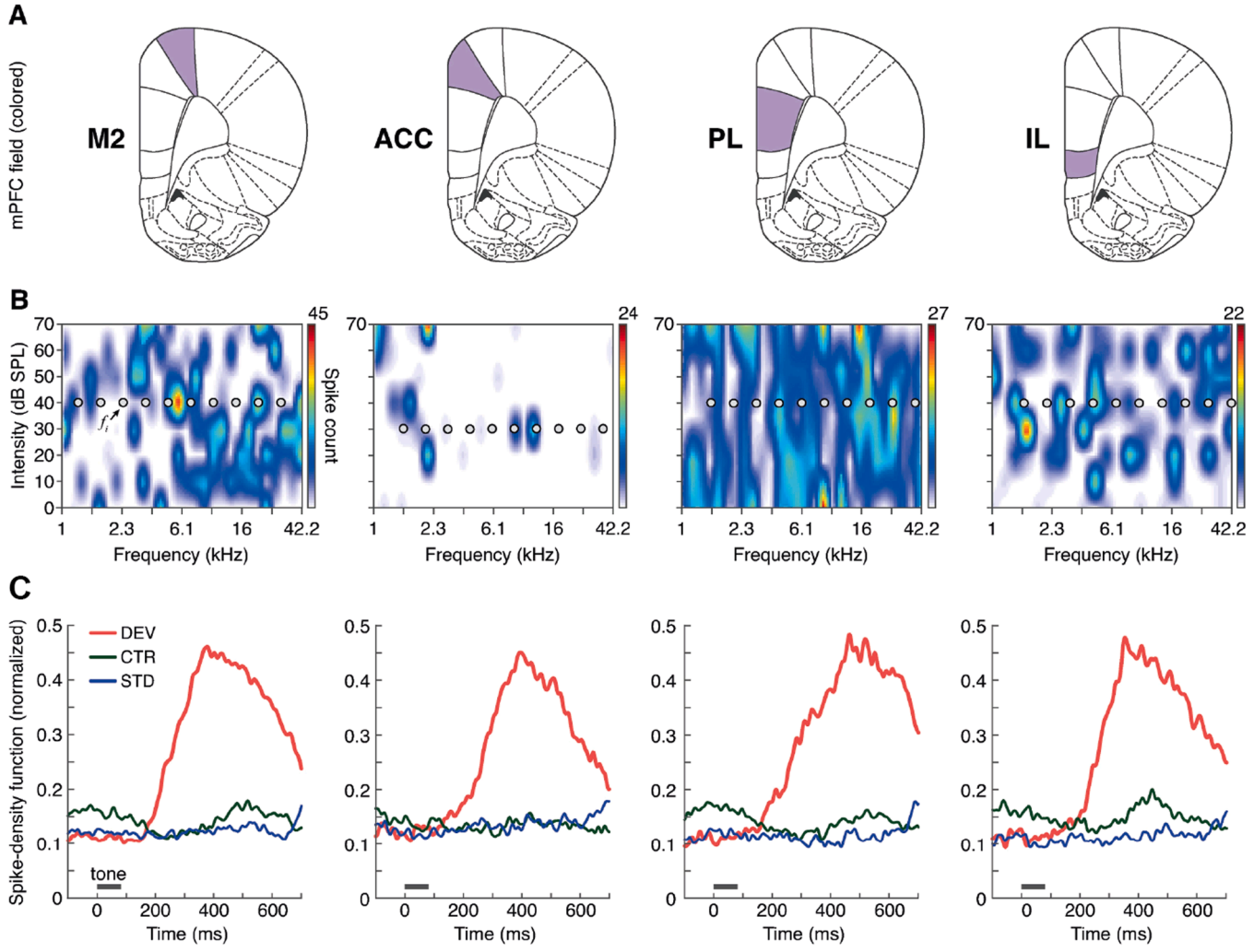

Fig. 2. Neural responses throughout the rat mPFC in response to predictable or unpredictable auditory tones. A) Schematic representation of rat mPFC coronal sections, highlighting each subdivision. B) Frequency response area plots of mPFC multiunit activity for the 4 mPFC fields as in A. No clear responses or frequency tuning are observed when 75 ms tones of randomised frequency and intensity combinations are presented. White dots represent frequencies chosen for further study in the original paper. C) Average neural firing rate profiles of each mPFC field in response to auditory oddball stimuli tones of 75 ms (black bars). Neurons throughout the mPFC do not respond to random auditory stimuli (CTR) or repeating stimuli (STD), however they have robust responses to unexpected stimuli (DEV). Figure adapted from Casado-Román et al. (2020), under Creative Commons 4.0 license.

6. Top-down auditory functions

6.1. Deviance detection

Mismatch negativity (MMN) is a biomarker for auditory deviant detection, whereby an auditory evoked potential to a rare deviant stimulus is greater than that in response to repeating standard stimuli. This response demonstrates how the brain encodes regular auditory patterns, generates an internal model to lower perception of regularities, and then detects deviations from these internal models (Fitzgerald and Todd, 2020). By drawing attention to unexpected stimuli, this processing mechanism is key for survival, however the mechanisms for its generation are still unknown. Stimulus-specific adaptation is commonly studied using an oddball paradigm, or repeating standard and rare deviant stimuli, and an index of neuronal mismatch (the presumed neural correlate of MMN), can be studied by recording neural activity (Parras et al., 2017). Neurons throughout the rat mPFC (M2, ACC, PL & IL) respond almost solely to deviant stimuli of an oddball paradigm (Fig. 2; Casado-Román et al., 2020). Furthermore, when no-repetition controls are used to determine the proportion of neuronal mismatch due to either repetition suppression or prediction error, it was revealed that mPFC neurons strongly encode prediction error (Casado-Román et al., 2020). Neuronal spike-rate levels to deviant stimuli are equivalent to deviant stimuli in the presence or absence of the repeating standards, demonstrating that during the oddball paradigm, the rodent mPFC is only encoding unpredictability.

Prefrontal coding of prediction has been confirmed in human intracranial ECoG recordings where using stimuli with “local deviants” (expectation established at short time scales <1 s) and “global deviants” (expectation established at long time scales 5–10 s) shows lack of PFC responses to deviant when the occurrence can be expected (Nourski et al., 2018). Furthermore, larger auditory-evoked to global deviants occur in prefrontal cortex during active listening, suggesting that task-modulation of auditory processing is occurring (Nourski et al., 2021). However, note that these human PFC studies are not specific to homologous areas of rodent mPFC.

Measures of neuronal mismatch and prediction error in the mPFC are a temporal match for the latency of the strongest MMN-like potentials (100–500 ms) (Casado-Román et al., 2020; Harms et al., 2014; Imada et al., 2012; Jodo et al., 2019), suggesting this is likely an analog for the human MMN generator in rat, and a true marker for prediction error. Therefore, in nuclei of the auditory pathway under top-down modulation from mPFC (i.e., AC), the spectral properties of acoustic stimuli are processed, and at mPFC only prediction error is processed. This may explain the latency disparities observed between the AC and the mPFC, where AC latencies to deviant pure tones are in the tens of milliseconds (Nieto-Diego and Malmierca, 2016; Parras et al., 2017), and mPFC latencies are in the hundreds of milliseconds (Casado-Román et al., 2020). Further, this suggests that AC and PFC processing occur sequentially, with spectral properties processed in AC, then prediction error based on context and abstract characteristics is processed in mPFC. This corresponds with the predictive processing hypotheses (Garrido et al., 2009), under which the top-down predictive activity in mPFC would inhibit AC responses to certain auditory input that are explained by the predictive model. Any unpredicted stimuli would therefore not be inhibited, and the larger prediction error responses would be conveyed bottom-up to update the model in the mPFC.

Prefrontal dysfunction underlies schizophrenia, in which patients show a variety of neuropsychiatric symptoms (Chini and Hanganu-Opatz, 2021). Schizophrenia patents also present reduced MMN, suggesting dysfunctional predictive processes, and auditory hallucinations; potentially a result of incorrect predictions (Bansal et al., 2018; Shergill et al., 2005). Therefore, the mechanisms underlying MMN and prediction control in the PFC are of great clinical interest and may be both a biomarker and target for treatment of symptoms of schizophrenia.

6.2. Attention

The mPFC also plays a key role in controlling selective auditory attention (Sharpe and Killcross, 2018). In a rodent selective attention task, it has been shown that pre-stimulus activity in the mPFC (and to a lower extent in AC), corresponds to the type of stimulus to be attended to (Rodgers and DeWeese, 2014). This pre-stimulus activity suggests that anticipatory activation in mPFC underlies attention to a specific stimulus, likely by altering AC activity. Furthermore, disruption of mPFC activity using transcranial magnetic stimulation impaired performance on a stimulus-selection task (Rodgers and DeWeese, 2014). A more recent study demonstrated the mPFC encoding only the selected stimuli, whereas the primary auditory cortex can encode all stimuli or be altered by input of contextually information from the mPFC (Barbosa et al., 2023). This research therefore demonstrates that top-down inputs from mPFC to AC control population gating in the AC, allowing selection of task-relevant stimuli in the AC (Barbosa et al., 2023). Furthermore, a recent preprint has demonstrated that inhibition of the ACC-AC pathway can disrupt gerbil behavioural performance during a difficult listening task, suggesting that ACC may be key for perception when auditory effort is required (Anbuhl et al., 2023).

6.3. Auditory fear conditioning

Another important function of mPFC is in auditory fear conditioning and learning (Giustino and Maren, 2015). In standard behavioural testing of fear conditioning an innocuous conditioned stimulus (e.g. auditory tone) is presented simultaneously with an aversive unconditioned stimulus capable of producing a fear response (e.g. electric footshock). After repeated trials, presentation of the innocuous stimulus alone can produce a fear response. Fear conditioning involves top-down control over cortical and subcortical structures and has been most studied within the PL and IL subregions, where it is thought to control the expression and suppression of fear in rodents, respectively. IL areas play a role in fear conditioning, and can be modulated to bidirectionally alter behavioural fear conditioning and extinction (Dadkhah et al., 2021; Do-Monte et al., 2015). In comparison, PL areas have been confirmed to drive behavioural decisions during fear detection behaviour, where multi-site recordings revealed a functional PL-AC connection (Concina et al., 2018). Specifically, PL-AC gamma synchronisation is required to correctly differentiate between a new tone and a previously conditioned stimulus. Modulating inputs to the mPFC can also alter learning during an aversive associative learning task, for example a recent study has demonstrated this using specific optogenetic inhibition of the basal forebrain–mPFC pathway (Tu et al., 2022). The degree by which fear alters auditory perception is not entirely known, however fear can potentiate the acoustic startle (Davis et al., 1993), and fear can also modulate frequency discrimination acuity, an effect mediated by the AC (Aizenberg and Geffen, 2013).

6.4. Avoidance

The mPFC, and more specifically the ACC, has also been shown to be important during auditory-evoked flight behaviour. Sun and colleagues (Sun et al., 2022) measured mouse running responses in response to flight-evoking sounds. They showed that preceding a 5 s noise with a 0.5 ms air puff lowered the noise intensity at which flight responses occurred and increased the movement speed, demonstrating that animals use the somatosensory information of the air puff as a cue for an upcoming auditory stimulus (Sun et al., 2022). Neural recordings revealed that ACC neurons respond to the preceding air puff, and AC neurons show larger responses to noises preceded by the air puff. Further experiments using chemogenetic and bidirectional optogenetic modulation of the ACC-AC pathway during the behavioural test revealed that facilitation within the AC is due to direct enhancement of AC responses to the sound by inputs from the ACC (Sun et al., 2022). A

following study on whether this mechanism can produce long-term enhancements of AC responses found that the direct ACC-AC pathway could not. However, the indirect pathway via the lateral rhinal cortex could produce long-lasting enhancement of AC responses, and a corresponding long-term increase in speed and intensity threshold of flight behaviour (Liang et al., 2023).

6.5. Changes in hearing loss & tinnitus

Hearing loss produces a variety of effect in auditory mPFC pathways, including altered resting-state functional connectivity of the ACC-AC pathway (Xu et al., 2022) and changes to functional PFC-MGB connections characterised by increased inhibition (Kristin M. Barry et al., 2021; De Vis et al., 2022). Tinnitus is the perception of phantom sounds, and while it is most commonly caused by hearing loss, the precise neural mechanisms of tinnitus generation are debated (reviewed by Hockley and Shore, 2023). As a modulator of sensory cortices, the role of the mPFC in tinnitus has been an interesting area of study. Proposed cortical mechanisms involve disruption of sensory gating of auditory and limbic stimuli, which results in a failure to supress the altered activity following hearing loss. The altered activity is therefore transmitted up the auditory hierarchy to the auditory cortex, and perceived as a phantom sound (De Ridder et al., 2014; Rauschecker et al., 2010). As previously discussed, the mPFC can control auditory grating, based on task-relevant auditory stimuli (Barbosa et al., 2023). Another proposed cortical mechanism of tinnitus is related to prediction in the cortex. After tinnitus-like input to the auditory cortex there is evidence that the cortical predictive model is altered from predicting silence to predicting incoming sound (Sedley et al., 2019). This results in tinnitus patients showing reduced EEG response amplitudes to deviant stimuli increasing in intensity around the tinnitus frequency, demonstrating that the default prediction has been altered from silence to sound input. This mechanism could best explain the chronic nature of tinnitus, and the difficulty in finding reliable treatments. As shown by Casado-Román et al. (2019), the mPFC encodes prediction error, and likely uses the resulting predictive model to control perception in sensory cortices. The mPFC therefore may play a key role in tinnitus generation. Indeed, tinnitus patients have altered resting-state functional connectivity of the ACC-AC pathway (Chen et al., 2018) and transcranial magnetic stimulation of PFC (NB: not specific to mPFC) can alleviate behavioural tinnitus symptoms in guinea pigs (Amat et al., 2022; Zimdahl et al., 2021) and humans (De Ridder et al., 2013). The role of mPFC in tinnitus is therefore an important area of study, with potential future clinical applications.

7. Conclusion

This article summarises the role of the rodent mPFC in auditory processing, pointing to a role during complex listening environments when higher-order information about the stimuli are required. We focused on the rodent mPFC as these studies have allowed more detailed mapping of the circuitry and function of the mPFC, where they have revealed auditory inputs to, and outputs from, the mPFC. Further, these rodent studies have shown a range of functions for the mPFC in processing of auditory information. Detecting deviant stimuli, attention to behaviourally important stimuli, avoiding perceived dangerous stimuli, and associative conditioning of stimuli all involve processing in the mPFC and subsequent top-down modulation of the central auditory pathway. Following hearing loss, mPFC-auditory connections are altered, with potential to affect listening in difficult conditions. In tinnitus, that often results from hearing loss, the neural mechanisms of generation are still unknown, however the mPFC is implicated in theories that show promising data so far.

To conclude, despite not being a part of the traditional central auditory pathway and therefore not often studied in the auditory field, neurons of the rodent mPFC respond to complex information about sounds such as context, predictability and valence. Top-down modulation of the central auditory pathway from the mPFC then controls auditory perception in a behaviourally relevant manner.

CRediT authorship contribution statement

A Hockley: Writing – review & editing, Writing – original draft, Conceptualization. **MS Malmierca:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

No data was used for the research described in the article.

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