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Ferret as a model system for studying the anatomy and function of the prefrontal cortex: A systematic review

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ABSTRACT

There is a lack of consensus on anatomical nomenclature, standards of documentation, and functional equivalence of the frontal cortex between species. There remains a major gap between human prefrontal function and interpretation of findings in the mouse brain that appears to lack several key prefrontal areas involved in cognition and psychiatric illnesses. The ferret is an emerging model organism that has gained traction as an intermediate model species for the study of top-down cognitive control and other higher-order brain functions. However, this research has yet to benefit from synthesis. Here, we provide a summary of all published research pertaining to the frontal and/or prefrontal cortex of the ferret across research scales. The targeted location within the ferret brain is summarized visually for each experiment, and the anatomical terminology used at time of publishing is compared to what would be the appropriate term to use presently. By doing so, we hope to improve clarity in the interpretation of both previous and future publications on the comparative study of frontal cortex.

1. Introduction

The expansion of the human prefrontal cortex (PFC) provides complex evolutionary advantages. Yet, new insights into its structure and function are still being revealed, with many open questions about its evolution and comparative neuroanatomy. Central to this investigation is the use of model organisms. Yet, finding homologous structures to the human PFC in model systems has proven difficult, due to the ambiguity and complexity of the structure. To this point, the criteria for characterizing the PFC are still evolving with unresolved incongruencies between – and within - model organisms. For example, conclusions on comparative neuroanatomy between rodents and primates vary depending on the strategy employed to define the neuroanatomy of the rodent PFC. This has led to overlapping and repetitive nomenclature, that can cause confusion when interpreting results (Laubach et al., 2018).

Historically, there have been multiple strategies employed to define the PFC. Lesion experiments provided the earliest functional characterization of frontal cortex in animal models (Ferrier, Yeo 1884; Ferrier, 1886). The first cytoarchitectural definition of human and primate PFC was proposed by Brodmann, who observed a clear granular layer IV that was either underdeveloped or absent in other species (Brodmann, 1909). This finding led to the belief that the PFC was an evolutionary structure unique to primates (Preuss, 1995; Brodmann, 1909). This view, however, was later challenged by Rose and Woolsey in 1948 who proposed to define the PFC in non-primates as the cortical region that receives the strongest reciprocal subcortical projections from the mediodorsal nucleus of the thalamus (MD) (Rose and Woolsey, 1948). Based on this definition, PFC was accordingly localized in many species like rat, mouse, rabbit, cat, dog, nonhuman primates (for review, see Fuster 2015), and ferrets (Duque and McCormick, 2010). Other strategies for defining the PFC include identifying strong dopaminergic projections (Divac et al., 1978) and involvement of the region in spatial-delay tasks (Eichenbaum, Clegg, and Feeley, 1983). However, neither criteria are diagnostic, as dopaminergic neurons also innervate primate primary motor and premotor areas (Berger, Gaspar, and Verney, 1991) and lesions to prelimbic cortex in rats (thought to be equivalent to primate dlPFC) also impaired spatial delayed alternation in a T-Maze (Brito

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et al., 1982), but the effects were transient and more superficial than in primate studies (Delatour and Gisquet-Verrier, 2001). For a detailed analysis of the techniques historically employed to define the PFC, please see the review from Wise (2008) and Preuss and Wise (2022). Recognizing the complexity of providing diagnostic criteria for the PFC, it is understandable that confusion has arisen around neuroanatomical boundaries and terms.

The PFC of the domesticated ferret (*Mustela putorius furo)* is less studied when compared to lab rodents, but has proven to be an advantageous model, e.g., for *in vitro* and *in vivo* investigation of prefrontal neurophysiology. A comprehensive summary of what is currently known about the ferret PFC is missing from the literature and provided here. There are several key advantages to studying FC neurobiology in the ferret that are exemplified in the following papers. Firstly, the ferret enables an electrophysiological investigation of neural dynamics that is more translatable to humans than similar studies done in rodents. This is because ferrets have clearly characterized task modulated frontal theta and parietal alpha oscillations (Sellers et al., 2016; Huang et al., 2021; Stitt et al., 2018), whereas it is unclear how rodent alpha-like oscillations relate to observed alpha in humans, however work examining this relationship is ongoing (for more details see (Fakhraei et al., 2021; Einstein et al., 2017)). This is an important point as theta and alpha are both prominent oscillatory frequencies that are proposed to have complementary roles in cognitive control in humans (Riddle et al., 2020; Gratton, 2018). Thus, the interaction of theta and alpha frequencies during behavior in the ferret could improve our knowledge on the role of FC in task-specific top-down regulation. Secondly, the ferret is an ideal model for neurodevelopment, because they are an altricial species and undergo cortical folding postnatally (Kazuhiko Sawada and Watanabe, 2012), allowing for a close investigation of mechanisms of the prolonged development of the PFC. The connection between neurodevelopment and cognitive impairments is an interesting and important question to keep pursuing as a research community, as our understanding that environmental influences effect brain development – especially PFC development - is increasing (Tooley, Bassett, and Mackey, 2021). Thirdly, the ferret, as a general carnivore animal model with complex cognition, is a cost-effective alternative for non-human primate research (Ball, 2006). And finally, methodology primarily developed in a rodent model (i.e. optogenetics) is more easily translatable to a ferret brain than a much larger non-human primate brain. (Shen et al., 2020; Galvan et al., 2017). This systematic review summarizes current research studies characterizing the anatomical and functional properties of the prefrontal and/or frontal cortex in ferrets. Four electronic databases (PubMed, Embase, Biosis Citation Index, bioRxiv) were searched for studies relating to the "ferret prefrontal/frontal cortex." Results and methods of the identified studies are summarized to describe the current knowledge in the field and identify gaps in knowledge to address in future studies. Nomenclature used to describe the location of experimental manipulation within the FC in functional studies are summarized with recommendations for updated terminology based on most recent findings. Future directions are proposed to further characterize and define ferret PFC within FC with the overall goal to advance fundamental and translational neuroscience research.

2. Summary of existing research

It is important to note that while referencing the reviewed papers, the terms to describe the experimental site were kept consistent with what was reported in the paper being discussed. Introduction and suggestions of updated terminology are presented in Table 1 for consideration when comparing between studies and integrating the presented information. Fig. 1 is included to illustrate the location terms. Table 1 refers to and shows an atlas-based reconstruction of the targets in ferret frontal cortex according to the referenced research papers with localized recording sites. Only a few studies with anatomical localization are available to date. Most recording sites were localized in premotor cortex (PMC), some at the border of caudal dorsal prefrontal cortex (dPFC) and rostral PMC (dPFC-PMC-junction) and only two clearly in dPFC.

Table 1
Re-evaluated nomenclature for anatomical localization of prefrontal recording sites in the ferret. All available terminology was extracted from referenced text and figures included in the paper. Recommended nomenclature is informed by ferret brain atlas (Radtke-Schuller, 2018). dPFC; dorsal prefrontal cortex, dlFC; dorso-lateral frontal cortex (includes dPFC and rostral PMC), PMC; premotor cortex, ASG; anterior sigmoid gyrus, OBG; orbital gyrus, PRG; proreal gyrus.

Publication	Terminology used in text (visual representation)	Atlas conform Nomenclature
Yin et al. (2020)	dlFC (figure)	PMC
Bagur et al. (2018)	dlFC (no figure)	dPFC and dorsal PMC
Wollstadt et al. (2015);(2017)	2015: PFC (no figure); 2017: PFC (cartoon)	2017: PMC
Sellers et al. (2016)	prefrontal cortex (figure)	Border of caudal dPFC and rostral PMC (dPFC-PMC-junction)
Zhou et al. (2016)	dl-FC (figure)	Border of caudal dPFC and rostral PMC (dPFC-PMC-junction)
Sellers et al. (2013); (2015)	2013: PFC (figure); 2015: PFC (figure)	2013: PMC; 2015: dPFC
Fritz et al. (2010)	PFC: dorsal OBG, rostral ASG (figure)	Three recording sites: One located in dPFC, two at the border of caudal dPFC and PMC (dPFC-PMC-junction)
Bimbard et al. (2018)	dlFC	dPFC and dorsal PMC

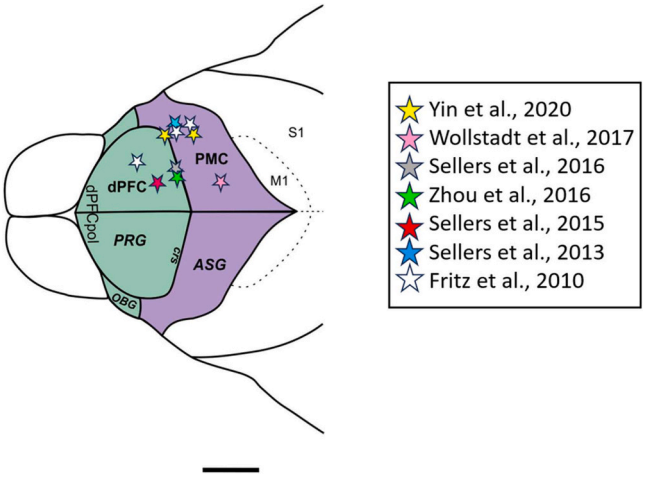

Fig. 1. Visualization of documented targeting in ferret frontal cortex. Atlas based reconstruction of targets in ferret frontal cortex according to the referenced research papers with localized recording sites. Only a few studies with anatomical localization are available to date. Most recording sites were localized in PMC, some at the border of caudal dPFC and rostral PMC (dPFC-PMC-junction) and only two clearly in dPFC. Scale bar: 3 mm.

2.1. Structural studies

2.1.1. Neuroanatomy

Generally, the human PFC is divided into dorsolateral (dlPFC), ventrolateral (vlPFC), orbitofrontal cortex (OFC) and medial/cingulate FC (MFC), each with both functional and anatomical distinctions (El-Baba and Schury, 2023). The primate FC contains agranular cortex (lacks internal granular layer 4), homotypical cortex (conspicuous layer 4) and dysgranular cortex (subtle layer 4) (Wise, 2008). The homotypical and dysgranular cortical regions are what is referenced when the term 'granular' cortex is used in Brodmann's earliest work, and corresponds to the primate dlPFC. The rodent, and all other non-primate

species, lack any homotypical or dysgranular cortex in FC, suggesting that there is no homologue to the primate. By contrast, agranular (limbic) PFC is shared by all mammals (for more detail see Todd M. Preuss and Wise 2022). The ferret PFC was outlined by Duque and McCormick (2009) by strong and reciprocal connections with MD. It can be subdivided into orbital PFC, corresponding mainly in the orbital gyrus, medial PFC (mPFC) covering the medial wall of FC (subproreal gyrus, pregenual gyrus and anterior cingulate gyrus) and a lateral/dorsal PFC (dPFC) situated on the proreal gyrus (PRG) of the FC (Radtke-Schuller, 2018). Distinct topographical projections from MD and other thalamic nuclei to the FC have led to the identification of three subdivisions anterior to primary motor cortex, that make up the dorsal FC (Radtke-Schuller et al., 2020). These regions include the PMC, the dPFC, with a newly proposed polar region of the dPFC, the polar dPFC (dPFCpol; listed caudal to rostral). To be compatible with previous nomenclature for the carnivore brain (for review, see Fuster 2015), PRG was introduced for the ferret. The PRG constitutes the anterior frontal lobe and mainly corresponds to the dPFC, medially bordering the medial FC (MFC) and ventrolaterally the orbital gyrus (OBG). The transition between dPFC in the posterior sigmoid gyrus (PSG) and PMC in the anterior sigmoid gyrus (ASG) can only be determined at the microscopic level and only to a certain extent, as the transition is gradual. Cortex in the ASG (PMC) appears more structured than PSG (dPFC), with large layer V pyramidal cells increasing towards the PSG, reaching their maximum size in motor cortex, as is observed in primates (Radtke--Schuller et al., 2020).

Each subregion of the ferret dPFC has distinct thalamic projection patterns that enable comparison to different primate regions. The PMC has large input from the ventrolateral thalamic nucleus (VL) (22% of total projections) that is not observed in the other two regions (2.4% and 7.6% for dPFCpol and dPFC, respectively) (Radtke-Schuller et al., 2020). This is as expected as strong VL input to motor areas is observed across species (Beloozerova and Marlinski, 2020). The thalamic connectivity of the ferret dPFC is comparable to the dorsal prefrontal regions in cats (Warren and Akert, 1964), dogs (Kosmal and Dabrowska, 1980; Narkiewicz and Brutkowski, 1967), and monkey (Warren and Akert, 1964; Goldman-Rakic and Porrino, 1985; Ray and Price, 1993; Erickson and Lewis, 2004; Fang, Stepniewska, and Kaas, 2006). The connectivity of the most rostral region, the dPFCpol, closely resembles what is observed in the fronto-polar cortex of non-human primates (Burman et al., 2011).

Discerning the PMC from dPFC in the ferret is difficult, as there is no cytoarchitectural landmark separating the regions, as was described earlier. In humans, the PMC represents a transition between the agranular motor cortex and the granular PFC. However, the distinction in the ferret has been more challenging due to lack of granular cortex and the strong projections from MD to both dPFC and PMC. Thus, the segregation of dPFC and PMC was not clear when Duque and McCormick originally described the boundaries of the ferret PFC (Duque and McCormick, 2010). It is now accepted that the PMC is primarily on the ASG, just anterior of the cruciate sulcus, and dPFC is located on the PRG, anterior to PMC (Radtke-Schuller et al., 2020) (Fig. 1). It is important to keep in mind that studies once thought to be investigating dPFC may have been reporting information from PMC or the border of the two regions (dPFC-PMC-junction), a side effect of an emerging field of study. In order to prevent future confusion, the following steps should be taken when reporting on experiments concerning ferret PFC: 1) Precise anatomical location should be included in the experimental design and clarified with coordinates referencing a published ferret brain atlas (Radtke-Schuller, 2018), 2) Anatomical terms relative to atlas location should be adopted in the text, and 3) Representative histology of the whole experimental region should be presented.

The connectivity of the ferret FC with the parietal cortex and temporal visual cortical areas has been investigated by Dell et al. (2019). A weak connectivity of the posterior parietal cortex (PPC) with motor cortex, PMC and orbital cortex of PFC was shown using biotinylated dextran amine (BDA). The connectivity of the PPC and FC is of particular interest, given these structures are functionally part of the frontoparietal attention network (Katsuki and Constantinidis, 2012; Ptak, 2012). The described connectivity of PPC with motor/premotor cortex, though weak, points to the existence of a frontoparietal network in the ferret.

2.1.2. Additional approaches

One alternative to tract-tracing experiments in descriptive neuroanatomy is identifying innervation patterns of subsets of neurons, including dopaminergic and serotoninergic neurons. Dopaminergic innervation patterns are a well characterized feature of the PFC ((Divac et al., 1978; Arnsten, Wang, and Paspalas, 2015; Gaspar, Stepniewska, and Kaas, 1992; Sesack and Carr, 2002)), and projection patterns have been included in comparative PFC literature (Preuss, 1995). In a similar way, serotoninergic innervation of the ferret cerebral cortex has been characterized and compared to other mammalian species (Voigt and de Lima, 1991). When comparing serotoninergic innervations between species, innervation density, pattern and contribution of different serotoninergic subsystems should be considered. For a detailed contrast of these characteristics between ferret, cat and non-human primates see Voigt and de Lima, 1991 manuscript. Researchers identified three distinct serotoninergic fiber morphologies. In most areas of the adult ferret cortex, innervation of serotonin-immunoreactive fibers was highest in layer 1 and decreased towards white matter. However, there were considerably different innervation densities between cortical areas. Specifically, serotoninergic fiber density in the PFC is significantly higher in supragranular layers compared to infragranular layers, as is observed in other model species (Voigt and de Lima, 1991).

A few of the above-discussed studies identifying anatomical connections of the ferret PFC brain have contributed to the ferret connectome project (www.ferretome.org), which was active approximately 2015–2020. This database includes macro-connectivity and architecture results from the ferret brain (Sukhinin et al., 2016), adapting and expanding on the methodology of the Collation of Connectivity data on the Macaque Brain (Stephan et al., 2001). The database is a valuable resource for future bioinformatic and experimental approaches to understanding the circuitry of the ferret brain. Unfortunately, the ferretome project is dormant until a new researcher with relevant interests assumes leadership.

2.2. Functional studies

In humans, it is appreciated that the interconnectedness of the PFC with other brain regions supports and regulates processes relating to cognitive control and executive function, including working memory, attention, motivation and emotion (N. P. Friedman and Robbins 2022; Teuber, 1972). Recent progress in training ferrets to perform complex behavioral tasks has enabled studies of frontal network dynamics during cognitive function. Ferret dPFC activity has been studied across spatial scales, from single-cell recordings in slice preparation to multisite recordings in the awake, freely moving animal.

2.2.1. In vitro and slice physiology: local brain circuits, cell propagation, and microcircuits

There is substantial ferret *in vitro* and slice physiology literature characterizing the balance of excitation and inhibition in local prefrontal cortical circuits (Haider et al., 2006; Sanchez-Vives et al., 2010), the affects of dopamine on prefrontal microcircuits (W.-J. Gao, Wang, and Goldman-Rakic, 2003; W.-J. Gao and Goldman-Rakic, 2003), and how prefrontal pyramidal neurons respond to common pharmacological interventions for schizophrenia, including Clozapine (W.-J. Gao, 2007; Rebollo et al., 2018). Additional studies discuss the contribution of calcium release to neocortex activity (W.-J. Gao and Goldman-Rakic, 2006), how prefrontal pyramidal cells support recurrent excitation during working memory (Winograd, Destexhe, and Sanchez-Vives, 2008), and provide insight on how Alzheimer's Disease pathology effects prefrontal neuronal circuitry (Wang et al., 2013).

Recent studies have added to the collection of research proposing that the imbalance of prefrontal excitation/inhibition contributes to the pathophysiology of psychiatric diseases with cognitive deficits, including schizophrenia (full review see: (Liu et al., 2021)). Furthermore, N-methyl-D-aspartate receptor (NMDAr) hypofunction is a common model of schizophrenia, as reduced NMDAr activation disrupts excitation/inhibition balance and alters gamma synchronization. An experiment in ferret prefrontal cortical slices was designed to determine if local prefrontal networks could replicate this phenomenon *in vitro* (Rebollo et al., 2018). An NMDAr blockade in ferret prefrontal cortical slices resulted in a beta-gamma frequency hypersynchronization, as is observed in schizophrenia, and implies that at least in part, features of schizophrenia persist in local circuits without long range cortical or subcortical connections. Additionally, Clozapine decreased the resulting hypersynchronization from the blockage in the local circuit, identifying a potential mechanism by which Clozapine attenuates symptoms of schizophrenia resulting from NMDAr hypofunction. This finding agrees with an earlier study that determined Clozapine inhibited spontaneous network synchronization, primarily by reducing persistent pyramidal cell excitation (W.-J. Gao, 2007). It was further determined that Clozapine enhanced pyramidal cell inhibitory inputs. These results together suggest that Clozapine may reduce symptoms of schizophrenia in part by adjusting the excitation/inhibition balance of prefrontal cortical circuitry.

To investigate the mechanisms of how dopamine acts on local excitatory circuits, dual whole-cell recordings were carried out in pyramidal cell pairs in ferret PFC in the presence and absence of dopamine (DA) (W.-J. Gao, Wang, and Goldman-Rakic, 2003). This study is important as the efficacy of antipsychotic pharmacological treatments of schizophrenia, like Clozapine, is dependent on the ability of the drug to block dopamine receptors, which support the hyperactivity observed in schizophrenic pathology. It was concluded that haloperidol, a D2 antagonist, reduced DA mediated burst firing in pyramidal cells (Wang et al., 2004). Further, a D4 antagonist that was not previously proven clinically effective, did not prevent DA-promoted bursting. This study demonstrates that excitatory effects of DA are mediated mainly via D2 receptors, adding to what is known about the mechanism of the antipsychotic effects of common treatments for schizophrenia.

While it was previously shown that dopamine depresses pyramidal cell excitatory transmission (W.-J. Gao, Wang, and Goldman-Rakic, 2003), paired recordings in ferret PFC were completed to determine the effect of dopamine on excitatory transmission between prefrontal pyramidal cells and fast-spiking (FS) interneurons. It was found that while dopamine did not affect FS interneuron excitatory transmission, it did enhance the excitability of FS interneurons significantly. This leads to the conclusion that the effect of dopamine on excitatory transmission is target specific and dependent on the microcircuit organization.

The intracellular mechanisms that support persistent excitation among pyramidal neurons in the neocortex were further investigated (W.-J. Gao and Goldman-Rakic, 2006). Findings in this study indicate that intracellular calcium release supports continued synchronized activity *in vitro*, and this calcium release is mediated through PLC-IP3 receptor pathway. Interestingly, these results also suggest that intracellular calcium release may contribute to the pathological synchronized activity observed in epilepsy *in vivo*. The contribution of calcium currents on neuronal spiking and neurotransmitter release in ferret layer 5 prefrontal cortical pyramidal cells has been further detailed (Yu et al., 2010). It was determined that voltage gated Ca^{+2} channels in the axon initial segment influences axonal action potential repolarization and increased neuronal excitability. This finding is significant, as it demonstrates a novel mechanism for how calcium currents influence neocortex electrophysiological activity, as previous work has focused primarily on presynaptic calcium channels.

Working memory describes the ability to hold task-relevant, sensory information for a prolonged period of time in order to carry out tasks. The PFC is a key neocortical region to supporting this cognitive function, however it remains unknown how prefrontal pyramidal neurons are interconnected to support working memory (Goldman-Rakic, 1995). Distinct pyramidal subnetworks with heterogenous synapses were identified via multi neuron patch clamp recordings in the ferret PFC (Wang et al., 2006). These subnetworks were observed to possess properties similar to pyramidal networks in primary sensory areas and contain complex pyramidal cell types and intricate connections. The identified subnetworks are thought to support persistent activity in the PFC by amplifying pyramidal cell interactions. It has further been shown that local circuit neurons in the PFC coordinate inhibitory mechanisms that shape the organization of neurons that are recruited in working memory tasks (F. A. Wilson, O'Scalaidhe, and Goldman-Rakic, 1994; Rao, Williams, and Goldman-Rakic, 1999; 2000). Excitatory input of local medium and wide arbor interneurons was identified in prefrontal microcircuits of ferret PFC (Krimer and Goldman-Rakic, 2001). The varying span of interneuron axonal arbors indicates the large number of neuronal circuits that these neurons could potentially regulate. However, these interneurons also have variable excitatory synaptic input and distinct physiological properties in addition to arbor width, suggesting that prefrontal microcircuits are highly organized to shape the input and subsequent activity of prefrontal pyramidal cells. This work provides critical insights into the specific network and subnetwork properties of the PFC that support working memory.

Sustained activity of pyramidal cells – which drives working memory – contributes to the enhancement in neural responsiveness, as shown in ferret *in vivo* slice electrophysiology (McCormick et al., 2003), building on previous work describing the mechanism of local excitatory circuit transmission modulation by dopamine, also in ferret prefrontal cortical slices (W. J. Gao, Krimer, and Goldman-Rakic, 2001). These results indicate that recurrent network and feedback mechanisms have a significant influence on neuronal responsiveness via synaptic bombardment that results from continuous activity. The effects of synaptic barrages have been investigated in intracellular recordings of layer 5 pyramidal cells in ferret prefrontal and visual cortical slices (Shu et al., 2003). Researchers showed that enhanced neuronal responsiveness (i.e., increased timing precision of action potentials) was achieved after balanced barrages of both excitatory and inhibitory synaptic activity.

Neural synchronization is essential to many cognitive processes and can be studied by examining the electrotonic coupling of cells. Previous work has demonstrated that synaptic connections are specific to cell type in inhibitory neurons (Gibson, Beierlein, and Connors, 1999), which allows for the formation of distinct networks that synchronize inhibition in the neocortex (Beierlein, Gibson, and Connors, 2000). To assess if pyramidal cells demonstrated similar methods of synchrony, electrotonic coupling was observed among paired pyramidal cells (PCs) in rat and ferret medial prefrontal and visual cortical slices (Wang, Barakat, and Zhou, 2010). Results demonstrated for the first-time special features of PC electrotonic coupling not observed in inhibitory interneuron gap junctions, which allowed perfect synchronization of action potentials between paired PC's in mPFC and visual cortex. This finding suggests that electrotonic coupling of PCs contributes uniquely to synchrony of neuronal assemblies and to the overall organization of the neocortex.

The PFC is an Alzheimer's disease (AD)-vulnerable region. Significant reduction of synapses in the PFC are observed in early AD pathology (Davies et al., 1987; Morris and Baddeley, 1988). The effect of concentration and species of beta-amyloid on excitatory post-synaptic potentials of single connections was investigated in ferret PFC slices (Wang et al., 2013). Their study revealed a concentration dependent inhibition of synaptic transmission for certain beta-amyloid species and suggested that beta-amyloid species can modulate both facilitating and depressing synapses in PFC. This work provides evidence that beta-amyloid disrupts single excitatory synaptic connections in the PFC through multiple mechanisms.

Together, these findings demonstrate the success and significance of *in vitro* investigations of prefrontal circuitry and network dynamics in

ferret PFC.

2.2.2. Anesthesia

A large amount of systems neuroscience research has been conducted on anesthetized animals, mostly for practical considerations such as recording quality and reducing the heterogeneity in sensory representations due to endogenous state changes in awake animals. While originally thought to suppress overall brain activity (E. B. Friedman et al., 2010; Steyn-Ross, Steyn-Ross, and Sleigh, 2004), anesthesia is now appreciated to impact local cortical networks in a region- and layer-specific manner (Lewis et al., 2012; Sellers et al., 2013; 2015). Several studies of the PFC-V1 (anterior-posterior) cortical network in the anesthetized ferret contributed to a network-level understanding of anesthesia (Sellers et al., 2013; 2015). First, it was hypothesized that anesthesia would impact network dynamics differently in the PFC and primary visual cortex (V1) given the differing functions of the two structures. This was found to be the case, as PFC spectral power was substantially altered uniformly across cortical layers, while modulation of activity in V1 by anesthesia was less pronounced and specific to layer IV (Sellers et al., 2013). Second, within the same network, the effects of sensory processing under anesthesia were examined via multiunit activity and LFP recordings in PFC and V1 during sensory stimulation. Reductions in functional PFC-V1 connectivity, disruption of sensory-evoked response duration, reduced PFC sensory response and V1 interactions, and altered response dynamics across cortical layers were observed in multiunit and local field potential analysis. This disruption was observed across cortical layers. These results demonstrate that network dynamics are significantly altered under anesthesia (Sellers et al., 2015). These findings suggest that examining functional brain networks activated by sensory input may lead to different conclusions in the anesthetized and awake animal.

The mechanism underlying the loss of consciousness under anesthesia has been suggested to be due to decoupling between brain areas, however this hypothesis fails to consider region-specific decreases in amount of information available. An alternative interpretation is that the rate of information transfer is directly affected by the amount of information present (Wollstadt et al., 2015; 2017). To test this hypothesis, local field potentials were simultaneously recorded in the head-fixed ferret ASG/PMC and primary visual cortex (V1) under titrated isoflurane levels (0.0%, 0.5%, and 1.0). Transfer entropy (TE) was computed as an index of information transfer between PMC and V1. A reduction in PMC-V1 TE was observed, with a stronger decrease in the top-down direction (PMC to V1). Signal entropy was evaluated by Lempel-Ziv complexity (LZC) and was also reduced. Additionally, local activity became more predictable, as evident by active information storage (AIS), an indicator of predictable information (Wollstadt et al., 2015). To further investigate if decoupling between brain regions is the employed mechanism for loss of consciousness induced by anesthesia, an additional study was conducted in similar experimental conditions to identify changes in locally available information (signal entropy) (Wollstadt et al., 2017). A strong reduction in source entropy of PFC and V1 was observed, with more significant reduction in PFC. The information transfer between V1 and PFC was reduced bidirectionally, however the effect was stronger top-down (Wollstadt et al., 2017). These results indicate that under isoflurane, changes in information transfer appear to be due to changes in local processing rather than decoupling between previously connected brain regions. A follow-up study developed an algorithm to measure information transfer/transfer entropy and validated the novel approach by describing information transfer between ferret PFC and V1 (with information from PFC to V1 oscillating at lower frequencies (4–8 Hz) and bottom-up information at higher frequencies (>125 Hz)) (Pinzuti et al., 2020). These results inform the conclusion that inter-area information transfer is reduced under anesthesia. Further, this reduction is in part caused by local entropy decrease, demonstrating the utility of quantifying information processing to comprehensive network analysis.

2.2.3. Cognition and Behavior

Ferrets have been trained in sophisticated behavioral tasks to identify network dynamics and connectivity during various dimensions of cognition, primarily through *in vivo* electrophysiology. The role of top-down signaling in perceptual difficulty was investigated in the ferret during a visual discrimination task. A majority of neurons recorded from the dorsolateral frontal cortex (dlFC) exhibited a preference for hard trials in a task difficulty paradigm, with increased spiking activity restrained to task-relevant epochs (Zhou, Yu et al., 2016). This finding adds to the existent human neuroimaging (Sigman et al., 2005) and single cell recording in primate literature that demonstrates task demands can reorganize top-down signaling (Asaad, Rainer, and Miller, 2000; Kveraga, Ghuman, and Bar, 2007). Further, suppressing pyramidal cells in the dlFC with ArchT silencing opsin led to reduced task reaction time (Zhou, Yu et al., 2016). These results suggest that single cells in the dlPFC are recruited for high-perceptual difficulty in visual discrimination tasks, contributing to top-down behavioral inhibition necessary for successful task completion. Further exploration of differential recruitment of FC depending on perceptual and cognitive difficulty would be very advantageous in the ferret, as groups have reported successful visual (Lempel and Nielsen, 2019; Dunn-Weiss et al., 2019) and auditory (Atiani et al., 2009) task difficulty paradigms that elicit adaptive differences in neural activity in the ferret.

The frontoparietal network of the ferret (PFC and PPC) displays a task-dependent theta synchrony during a preclinical sustained attention task (Sellers et al., 2016). This synchrony was mediated by local and long-range locking of spiking activity to primarily theta and high-gamma oscillation frequencies. Additionally, parietal alpha suppression was observed during the sustained attention period of the preclinical task (Sellers et al., 2016). In humans, increased functional connectivity of the frontoparietal network and engagement of theta oscillations is observed during sustained attention behavioral tasks (Scolari, Seidl-Rathkopf, and Kastner, 2015; Buschman and Miller, 2007). Parietal alpha is also a marker of attention in humans (Deng et al., 2019; Misselhorn, Friese, and Engel, 2019), and rodents do not have a clear parietal alpha peak frequency. Thus, the ferret is an ideal model to study the network dynamics and connectivity of sustained attention. Further, optogenetic experiments to enhance or reduce certain oscillatory features thought to drive the frontoparietal network during sustained attention, may be able to identify targets for treatment of attention deficits with non-invasive brain stimulation.

The top-down dynamics of the dlFC and primary auditory cortex (A1) during a variety of auditory cue tasks have been studied extensively in the ferret. Neurons recorded from PMC and PFC differentially fire to task-relevant stimuli in auditory task, potentially determining a mechanism for continuous task-related plasticity (J. Fritz, Elhilali, and Shamma, 2005). The influence of PFC activity on A1 neurons could be a result of direct or indirect pathways from PFC to A1 (J. B. Fritz, Elhilali, and Shamma, 2004). These results were supported in an additional study that demonstrated FC and A1 form a functional connection during auditory behavior, and that FC neurons were behaviorally gated and encoded task-timing (J. B. Fritz et al., 2010). Single unit recordings from this study were compared to recordings from the higher auditory cortex, the dorsal posterior ectosylvian gyrus (dPEG) during auditory behavior. Neurons from the dPEG recordings demonstrated both the sensory responses observed in A1 and the task-related plasticity observed in the dlFC. This study showed that the dPEG could be a part of the information transfer between the A1 and dlFC (Atiani et al., 2014). Additionally, it has been shown that neuronal responses become more categorical in higher cortical fields during auditory behavior tasks, and this response follows a top-down modulation pattern from the dlFC to tertiary, secondary and primary auditory cortex (Yin et al., 2020; Elgueda et al., 2019). During engagement in a Go/No-Go auditory task, electrophysiology recordings demonstrated that target-specific patterns of activity in the A1 and dlFC are similar, potentially indicating that sound-evoked A1 activity triggered dlFC activity that feeds back top-down inputs to A1

(Bagur et al., 2018). To test this idea, a model of functional connectivity designed for analysis of rapid task-dependent spiking activity (Granger Causality inference) was applied to single-unit data from simultaneous recordings of A1 and dlFC in the ferret, during passive listening and active auditory task conditions (Sheikhattar et al., 2018; 2016). This analysis provided evidence that supports the functionally dynamic relationship of top-down and bottom-up neural activity in the ferret A1 and dlFC during attentive auditory behavior. For detailed description of the development and use of this model see (Sheikhattar et al., 2018; 2016).

Functional ultrasound (fUS) has been used to map the functional connectivity between the ferret frontal and auditory cortices (Bimbard et al., 2018). fUS provides information on brain activity by imaging cerebral blood volume changes (Mace et al., 2013) at high acquisition rates that can discriminate blood flow from motion artifact (Demené et al. 2016). To demonstrate the ability of fUS to capture connectivity of distant brain regions, researchers delivered 2 millisecond electric stimulation pulses (200 ms-long train repeated at 2 Hz) to various locations within the FC and recorded the evoked hemodynamic responses in the auditory cortex. In brief, evoked activity was observed in insular cortex of the pseudosylvian sulcus (PSSC/insula), whereas no evoked activity was observed in secondary auditory areas. Validation of anatomical connectivity was carried out using virus tracer (for more detail see (Bimbard et al., 2018)). A main benefit of the technique is its extended field of exploration. Thus, fUS can be an advantageous tool for further characterizing functional connectivity between the ferret frontal cortex and other sensory cortices.

2.2.4. Development

A comprehensive understanding of PFC development is critical to designing therapeutic strategies for neurodevelopmental disorders, and there are several strong advantages of studying this in the ferret. Firstly, the ferret is the smallest laboratory animal with an expanded and folded neocortex, which is considered an evolutionary feature that supports advanced cognitive abilities (Fernández, Llinares-Benadero, and Borrell, 2016; Sousa et al., 2017). Secondly, cortical folding (gyrification) occurs postnatally in the ferret (Barnette et al., 2009; Kazuhiko Sawada and Watanabe, 2012). Multiple researchers have leveraged this developmental feature and described the gyrification of the ferret cerebral cortex. One study correlated the external developmental stages to internal changes through a histological analysis of ferret cerebral cortex postnatally until adulthood (Smart and McSherry, 1986). Differences in gyrification between male and female ferrets has also been described via MRI-based morphometry (K. Sawada and Aoki, 2017). Researchers observed the sexual dimorphism was age-related and biphasic. Another group discovered that neurons involved in cortical folding in the prefrontal, parietooccipital and cingulate regions – components of the evolutionally-expanded cortex – were born later in neurogenesis, from self-renewed neuronal stem/progenitor cells (Kazuhiko Sawada, 2019).

Logistically, complex developmental processes occurring post-utero allow a close examination of developmental stages via advanced imaging such as MRI. This advantage has been illustrated in the development of the Ferret Integrative Imaging Neurodevelopmental atlas (FIIND), an online atlas of the complete development of the ferret brain. This resource will be helpful for designing future PFC developmental studies in the ferret. Additionally, postnatal cortical interneuron integration to cortical regions is observed in the ferret, unlike rodent species (Ellis et al., 2019). This finding indicates that the ferret is a suitable model organism for studying the migration of immature interneurons to cortex, a key process of early neurodevelopment in humans. In addition to basic neurobiology, the relatively short gestation period (45 days) and large litter size (5–8 kits) of the ferret also makes them a desirable laboratory model. For a full review on the advantages of studying neocortex development in the ferret see the review by Gilardi and Kalebic (Gilardi and Kalebic, 2021).

Strong evidence supports the ferret as a model to study disorders with a neurodevelopmental origin (Li et al., 2018). For example, the effect of maternal immune activation (MIA) on social behaviors, brain oscillations and gut microbiome has been investigated in the ferret. Maternal illness during pregnancy has been associated with a higher risk of psychiatric disorders such as autism spectrum disorder and schizophrenia (Grabrucker, 2012; Murray et al., 2017; Mednick et al., 1988). This study confirmed what was previously known about MIA via rodent studies, which have been used to model schizophrenia. Researchers took advantage of previous findings that ferrets display various socio-cognitive functions and studied a wide variety of behaviors including eye contact tolerance and engagement with salient stimuli (Li et al., 2018). Ferrets have also been used as a model to test the relationship between Valproic acid (VPA) – common treatment for autism spectrum disorder – and gyrencephalic abnormalities (Kazuhiko Sawada, Kamiya, and Aoki, 2021). MRI-based morphometry was performed *ex vivo* and demonstrated that ferret pups who were exposed to VPA neonatally showed significantly less global gyrification primarily in the frontal and parietotemporal cortex. Further, multisensory processing deficits have been associated with individuals with fetal alcohol spectrum disorders (FASD). A study in which ferrets were exposed to ethanol during developmental periods experimentally determined if brain volume differences were observable post ethanol exposure, particularly in sensory cortices. Researchers showed that whole brain volume was reduced with ethanol exposure, however frontal brain area was larger compared to controls (Tang et al., 2018). It was proposed that this increase in frontal volume could have been due to less pruning (Sowell, Thompson, and Toga, 2004; Toga, Thompson, and Sowell, 2006). Lastly, the ferret genome has been sequenced (Peng et al., 2014) and can serve to direct genetic investigations of neurodevelopmental disorders with genetic components.

Ferrets are also a popular animal model for studying respiratory diseases (Mednick et al., 1988). In 2012, researchers investigated neurological signs of highly pathogenic avian influenza A (HPAI) in ferrets. Expression was detected throughout the frontal cortex and cerebrum. It was proposed that increased lethality could be due to increased replication in brain regions highly involved in higher order function. Ferrets have also played an integral role in understanding various aspects of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)(Kim et al., 2020). Ferrets are an advantageous model of SARS-CoV-2, as they share coughing and sneezing reflexes with humans (Cameron et al., 2012) and can rapidly transmit the disease through physical contact or aerosols (Kim et al., 2020). For a detailed review on the most recent applications of the SARS-CoV-2 ferret model to understanding the spread and expression of the virus, see (Zhao et al., 2023).

3. Discussion

Over the past 25 years, much has been discovered about the anatomical boundaries, connectivity, and functional properties of the ferret frontal cortex. The papers discussed in this review highlight the breadth of experimental questions related to human health that have been answered by investigating the frontal cortex in the ferret, with experimental methodology spanning all research scales. As more knowledge is gained, educated comparisons between the ferret and other model species can be made, deepening our understanding of the translational implication of experimental findings in the ferret. The key takeaways from the papers summarized in review include: (1) The ferret possesses neurophysiological characteristics that make them an advantageous model for studying a range of questions pertaining to the PFC/FC, (2) Researchers who start working with ferrets can be more informed and precise by building upon the significant amount of advanced science – highlighted in this review – that already exists, and (3) Thorough documentation and description of anatomical targets for research publications are needed for interpretation of the results in the future.

Anatomical tracing studies have led to the identification of the ferret dPFC and PMC subdivisions, through the analysis of thalamic-cortical

connectivity. The similar projection pattern from thalamic nuclei to dorsal frontal areas, specifically from the MD and VNG (ventral nuclear group of thalamus), observed in the ferret and non-human primate suggests that similar divisions previously made in non-human primates can be made to an extent also in the ferret (Badre and D'Esposito 2009; Romo and de Lafuente, 2013). To this point, MD projections to the ferret dPFC closely resemble what is observed in the dlPFC of the monkey (Warren and Akert, 1964; Goldman-Rakic and Porrino, 1985; Ray and Price, 1993; Erickson and Lewis, 2004). The distinction between cortical connections of the dPFC and PMC is an ongoing effort, with results potentially elucidating key functional differences between these regions to be further experimentally investigated. The proposal of the ferret dPFCpol region as a distinct region at the most rostral part of the brain, is supported by unique projections from MD subdivisions not observed in dPFC or PMC. Projections from these subdivisions are also observed to project to frontal polar cortex (BA 10) in non-human primates (Radtke-Schuller et al., 2020; Burman et al., 2011). Based on reported results, it is possible that this area integrates information from several high-level sensory processing systems. While an exciting possibility, future experiments are needed to determine if this parcellation is appropriate and what functions are attributable to the region.

The comparison of neuronal networks between the ferret and other model species is further supported by the identification of a resting state network via resting state functional MRI (rsfMRI), including a putative default mode network (DMN; (Zhou, Salzwedel et al., 2016)). As DMN connectivity is disrupted in many neuropsychiatric disorders, including schizophrenia (review; (Nair et al., 2020)), this finding not only supports the comparison of ferret neural networks with other species, but also demonstrates ferrets could be a useful model for providing insights into a range of psychopathologies.

Functional *in vivo* investigations of top-down sensory processing in the ferret have spanned much of the dorsal frontal cortex of the ferret (Fig. 1). As a detailed brain atlas (Radtke-Schuller, 2018) and additional anatomical tracing studies are published (Radtke-Schuller et al., 2020), it is important to revisit the terminology in previously published studies. Here, we review past studies that have reported a site of experimental manipulation in the ferret frontal cortex, and provide the most precise anatomical terms based on the current information (Table 1). The purpose of this report is to first reduce possible confusion about terminology when reading older papers and secondly to act as a guide for the level of precision in language that is needed for future publications.

As there are only a small number of publications on ferret frontal cortex and the precise location of the studies has been variable within the dFC boundaries, the functional differences between these frontal brain areas are unclear. Given that the frontal cortex has primarily been organized into subdivisions associated with distinct behaviors (monkey; (Teuber, 1972), human: (C. R. E. Wilson et al., 2010), anatomical-functional relationships should remain at the center of future ferret research.

3.1. Future Directions

Cognitive control requires the integration of information across many cortical regions to meet task demands (Hernández et al., 2010). Knowledge of these neural network nodes enables targeted investigation of dysregulated network activity in psychiatric disorders. Future experiments employing electrophysiology and optogenetic manipulation during behavior tasks are needed to identify the functional differences between FC subdivisions in the ferret. Pairing functional studies with neuroanatomical tracing will identify which neural networks each subregion engages with and when. For example, a recent electrophysiology study demonstrated that the dorsal PMC in monkeys has a larger role in decision making than previously thought (Diaz-deLeon et al., 2022). In addition to each FC subdivision, the transition between areas is also of interest. Before an atlas was developed that separated dPFC from PMC, many papers included data recorded from the border of the dPFC and PMC (Fig. 1), and reported significant brain and behavioral findings that have greatly advanced our understanding of top-down sensory processing. Therefore, we propose to refer to this region as the *dPFC-PMC-junction*, which will be used until this transitional area between dPFC and PMC is more clearly demarcated. The provisional term *dPFC-PMC-junction* will be useful when referencing older papers as well as reporting targeting in future publications.

Experimental investigations of the ferret frontal cortex have significantly contributed to multiple fields of neuroscience. Ferret neuroanatomical tracing studies provide detail on the similarities and differences in prefrontal thalamic connectivity between ferrets, rodents, non-human primates and other small mammals. Functional investigations demonstrate that the ferret is an advantageous model to study the neurophysiological underpinnings of sensory and cognitive function, top-down executive control, and neuropsychiatric disorders.

4. Methods

The protocol for this review was developed following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-P) **(**Fig. 2**)**. The protocol was developed by GR and reviewed by the principal investigator who is experienced in ferret neuroscience studies (FF).

4.1. Search strategy and study selection

Four electronic databases (PubMed, Embase, Biosis Citation Index, bioRxiv) were searched for studies relating to the "ferret prefrontal cortex" and "ferret frontal cortex." All data bases were preliminary searched the same day in June 2021, and a secondary search was completed in February 2023 prior to publication. Medical Subject Headings (MeSH) and free-text terms were developed with an expert librarian at the UNC Chapel Hill Health Sciences Library, and refined through discussions with members of the research team and FF. Results from each search were exported to EndNote, deduplicated and exported to Covidence for screening. Two reviewers collaborated on the title and abstract screening of 250 studies, guided by inclusion and exclusion criteria detailed below. Disagreements were resolved through discussion and further specification of eligibility criteria in line with the goals of the review. At the end, 52 studies were included (Fig. 2).

4.2. Eligibility criteria

Aiming to capture all research studies investigating the ferret PFC, inclusion was dependent only on the following: (1) the investigation took place in the brain of the ferret (*Mustela putorius furo*) and (2) the analysis included frontal and/or prefrontal regions. Studies in which the ferret was used in a secondary role (i.e., eliciting fear in rodents) or the primary brain region investigated was not a part of the frontal cortex were excluded. Each study that passed title and abstract screening also met inclusion criteria during full-text screening.

4.3. Data extraction

After careful review of the included studies, the following were identified as significant parameters to consider, and were subsequently manually extracted: structure or functional study and scale of research (i.e., *in vitro*, slice physiology, *in vivo*). Whether a study was focused on structure or function was determined based on overall hypothesis tested, reported results and methods employed. For example, a study utilizing anatomical tracers or tractography techniques to define PFC boundaries and compare with other model species were considered a structural, whereas a study that involved a behavioral task and/or electrophysiological investigation was categorized as a functional study. Scale of study was determined primarily in the methods section of the paper and in-text descriptions.

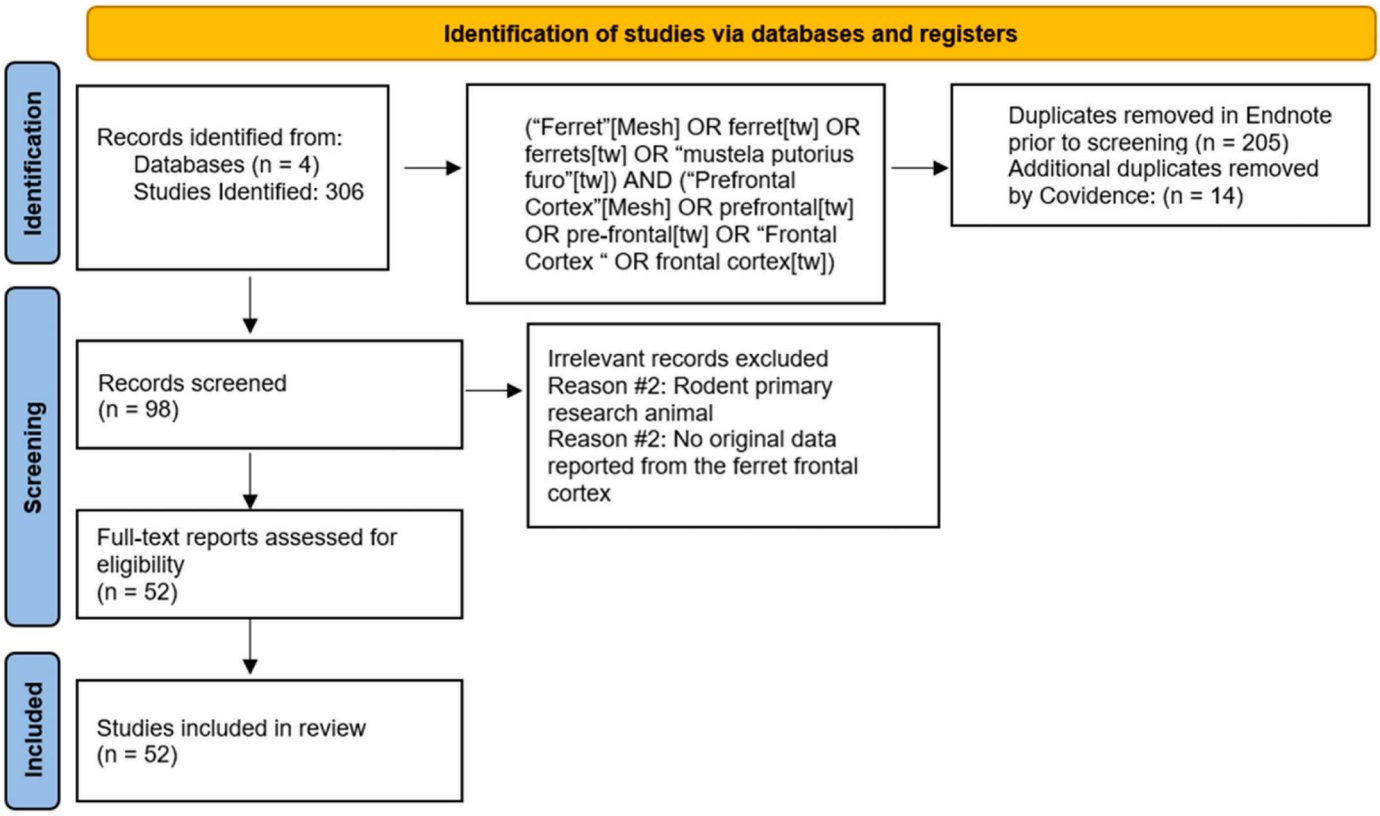

Fig. 2. Preferred reporting items for systematic reviews & meta-analyses flow diagram of the screening and inclusion of studies.

Disclosure

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