AN OVERVIEW: FUNCTIONALITY OF THE PREFRONTAL CORTEX

In relation to stress and memory

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Abstract:

The prefrontal cortex is a complex and substantial part of the brain. It mediates the control of multiple high-level cognitive behaviours. To better understand the functionality of this part of the brain, in this review, convergent research will be discussed to answer the question how the prefrontal cortex is involved in cognitive processes like decision making, the forming of memory, and the behavioural expressions associated with stress. To do so, an analysis of the neurophysiological components and contents of the prefrontal cortex is made. These components will be explored in the rodent model of stress and memory and will be examined with optogenetic tools. Results based on the functionality of the neurophysiology show a great involvement and connectivity of the subsets of the prefrontal cortex in processes as learning, decision making and the processing of sensory information and giving this information a value for projections to other areas of the brain. The newly developed tool of optogenetics showed that subsets of the behavioural output concerning the phenomena like stress and memory can be altered and sometimes even induced as a result of this optogenetic manipulation. The optogenetic tool and rodent model prove themselves important for future understanding and examining the functionality of the prefrontal cortex.

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Introduction:

The prefrontal cortex (PFC) mediates the control of multiple high-level cognitive and emotional behaviours in a top-down manner which means that it can affect other areas of the brain, a general phenomenon of the brain (Euston et al., 2012a). The PFC is responsible for the sensory information processing of memory, perception, and diverse cognitive processes (Goyal et al., 2008). Local processing in the PFC is driven by many long-range excitatory inputs that arrive from other brain regions (Hoover & Vertes, 2007; Miller & Cohen, 2001). The PFC itself can be subdivided in three main regions: the orbital (oPFC), the medial (mPFC) and the lateral (lPFC) prefrontal cortex (Fuster, 2001). The PFC is phylogenetically one of the latest areas to develop, having earned maximum relative growth in the human brain (Rakic, 2009). Knowing that this part of the brain has such a rich history in research together with the fact that the PFC does not attain its full maternity until adolescence or later on (Paus, 1999), the PFC is a most interesting and widely studied part of modern day neuroscience research.

In this review I will analyse the components and contents of the PFC, regarding the neurophysiology that is specifically involved in the forming of memory, making decisions and behavioural expressions associated with stress to answer the question how the prefrontal cortex is involved in those cognitive processes. By doing so I will provide an overview of the established knowledge about the functionality of the neurophysiology of the PFC. Therefore I will develop an answer based upon the latest research to the question how phenomena as memory and stress are explained by means of neurophysiology. I will pursue to find the answers regarding causation in those processes with animal (rodent) models and the newly developed method of optogenetics.

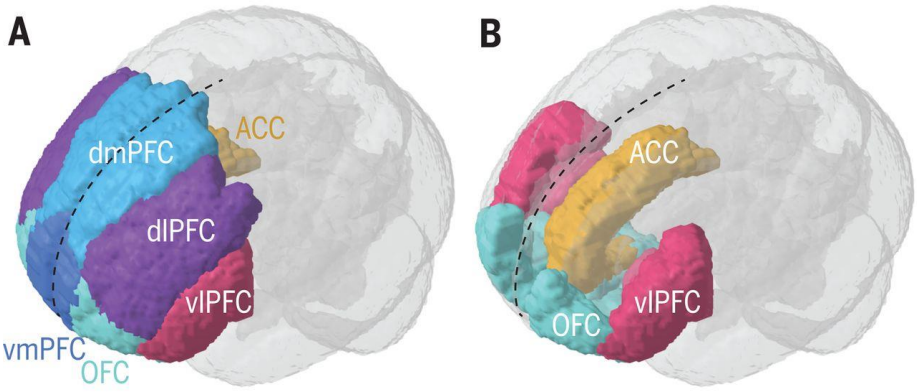

Figure 1: ***The distribution of the functional areas of the human prefrontal cortex.*** *(A and B) The frontal-view of the human brain with the illustrations of the common functional segments. The dashed black line demonstrates the sagittal midline. dmPFC: dorsomedial prefrontal cortex; dlPFC: dorsolateral prefrontal cortex; vlPFC: ventrolateral prefrontal cortex; vmPFC: ventromedial prefrontal cortex; OFC: orbitofrontal prefrontal cortex; ACC: anterior cingulate cortex. (*Adapted from *"What constitutes the prefrontal cortex?"* by M. Carlén, 2017, *Science*, *358(3662),* p. 478-482. Adapted with permission*)*

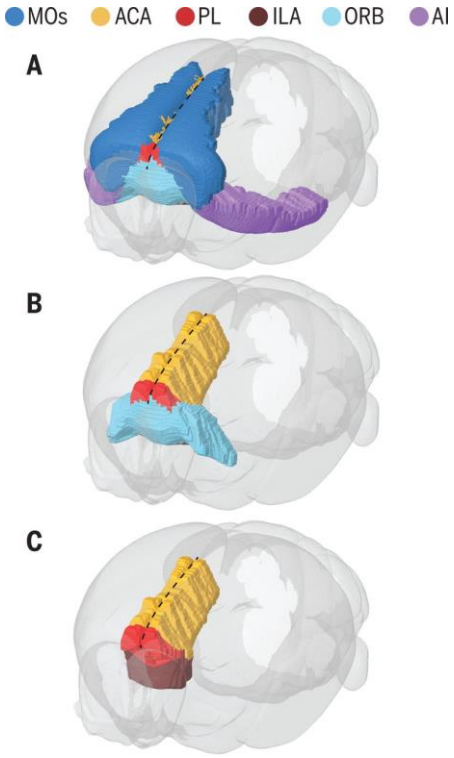

Figure 2: ***The distribution of the functional areas of the prefrontal cortex of the mice.*** *(A to C) The frontal-view of the brain of a mouse with the illustration of the common functional segments within the prefrontal cortex. (A) All areas, (B) with MOs removed, (C) with MOs and ORB removed. Dashed black line demonstrates the sagittal midline. MOs: secondary motor area; ACA: anterior cingulate area; PL: prelimbic area; ILA: infralimbic area; ORB: orbitofrontal area; AI: agranular insular area. (*Adapted from *"What constitutes the prefrontal cortex?"* by M. Carlén, 2017, *Science*, *358(3662),* p. 478-482. Adapted with permission*)*

Anatomical organization of the prefrontal cortex

The development of the frontal lobes patterns involves a dynamical, hierarchical process of multiple levels (Case, 1992). The PFC has many connections, such as the brainstem, the thalamus, the limbic system ass well with the basal ganglia. The functional role of the afferent connections that the PFC has can be derived from the functions of those structures (Fuster, 2001). The prefrontal cortex can be divided in the three main regions: the orbital-, the medial- and the lateral prefrontal cortex. I shall first briefly review the functional and anatomical properties of the prefrontal cortex for the purpose of understanding its role.

The orbital prefrontal cortex

The orbitofrontal cortex represents the value of stimuli, the reward received and therefore the expected value. It can be described as an output region for the sensory systems. It represents 'what' a stimulus is for sensory systems such as taste, olfaction, visual, auditory and somatosensory information (Rolls, 2019a). The orbitofrontal cortex receives from every sensory hierarchy

information about what taste, smell, vision, touch, visual- and auditory stimuli are present. The orbital prefrontal cortex is essential for the suppression of distractions in selective information processing between all those stimuli. There are a wide range of outputs of the orbitofrontal cortex: the cingulate cortex, striatum, inferior frontal gyrus, and indirectly via the habenula to the dopamine and serotonin neurons in the brainstem, which are shown in figure 4 (Rolls, 2019a). Thus, the projections of the orbital frontal cortex to those output-regions make it possible to represent those projections in terms of value per stimuli. (Rolls, 2019a).

The orbitofrontal cortex has a strong connectivity with the cingulate cortex, rewards are present in both the orbitofrontal cortex as in the cingulate cortex, both of which could be activated by hostile and positive rewarding stimuli (Cheng et al., 2018). A hostile stimulus is a stimulus that represents non-reward, this could be seen as an unpleasant or punishment-stimulus. The orbitofrontal cortex also has outputs that can influence autonomic functions via the hypothalamus, midbrain and the insula (Critchley & Harrison, 2013). To bring together information about the specific value of the reward with information about actions, and the costs associated with those actions, it is important for associating actions with their outcomes, especially considering the values of those outcomes. Then there could be a correct action chosen that will lead to a desired reward (Rudebeck et al., 2008). Thus, the orbitofrontal cortex plays a key role in the rating of a reward based on sensory input. Research showed that the orbitofrontal cortex only represents value but not the actions. It takes decisions based on the reward value, this information about the value is then transmitted from the orbitofrontal cortex to the anterior cingulate cortex. This is probably where the action related neurons are, and there the action-outcome of learning takes place (Cai & Padoa-Schioppa, 2012). Interestingly, the orbital prefrontal cortex also has a connection with the posterior cingulate cortex, which has strong connections with the hippocampal memory system through the connection of the entorhinal cortex (Bubb et al., 2017; Vogt & Pandya, 1987). This is important for the meaningful-related information from the orbitofrontal cortex that has access to the posterior cingulate cortex by this dorsal route into the hippocampal memory system. This could be the connection that gives meaning to memories based on sensory input (Rolls & Wirth, 2018). So, the anterior cingulate cortex receives information about reward and punishment outcomes, where the posterior cingulate cortex also has a connection with the orbitofrontal cortex via the dorsal routes (Rolls, 2019b, 2019c).

The orbitofrontal cortex and the amygdala are the systems which are involved in the reward- and non-reward routes and can operate through the basal ganglia route: the striatum, ventral pallidum, and globus pallidus routes. This influences the lateral habenula, which in his turn can influence dopamine neurons in the substantia nigra due to the GABAergic rostro-medial tegmental nucleus. This connectivity provide a few routes: a reward, a non-reward and a reward prediction error signal (Haber, 2014; Proulx et al., 2014). It has been found that goal values are correlated with activity in the medial orbitofrontal cortex, and positive reward prediction errors are correlated with activity in the nucleus accumbens (Hare et al., 2008).

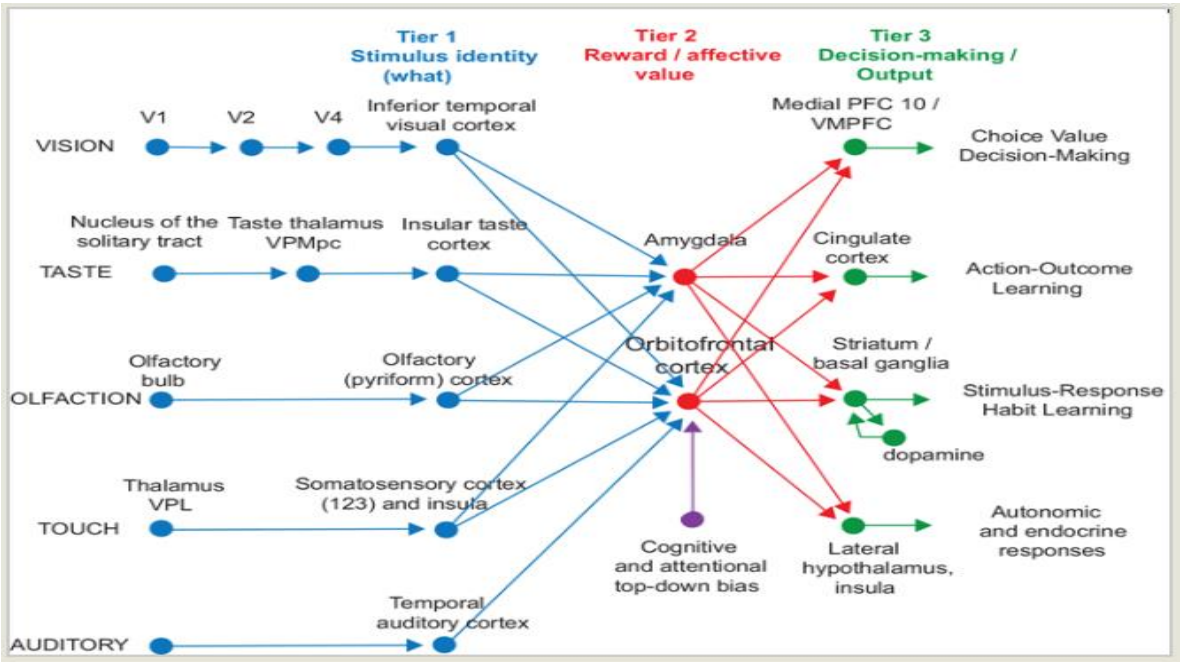

Figure 3: ***schematic diagram showing the connections of the taste, somatosensory, visual and auditory pathways to the orbitofrontal cortex and amygdala.*** *V1: the primary visual (striate) cortex; V2 and V4: further cortical visual areas; PFC: prefrontal cortex; VPMpc: ventro-postero-medial nucleus pars parvocellularis of the thalamus, which conveys taste information to the primary taste cortex; VPL: ventro-postero-lateral nucleus of the thalamus, which conveys somatosensory information to the primary somatosensory cortex. (*Reprinted from *The Orbitofrontal Cortex: anatomy and connections* (p. 3) by E.T. Rolls, 2019, Oxford University Press. Copyright 2020 by Oxford University Press. Reprinted with permission*)*

The lateral prefrontal cortex

The lateral prefrontal cortex has an important role in the complex system of value-based learning and decision making (Dixon & Christoff, 2014). Value based learning includes multiple steps of processing: the value of engaging rule-based cognitive control, the integration of multiple fragments of information, determining the best course of action, to pursue future rewards, the evaluation of abstract concepts, and comparing the value of the imagined alternative action against the executed action. So in contrast to habitual learning for rodents, which is based on repeated experiences, value-based learning includes a goal-directed system that consistently updates the value of an action as soon as the value of its outcome changes (Rangel et al., 2008).

There is strong evidence, found in human as in animal studies, that the rostral-caudal axis of the functional organization involved in this process lies within the lateral prefrontal cortex (Petrides, 2005). Lesion studies in monkeys suggested that the caudal dorsolateral prefrontal cortex has a critical role in the selection between different aspects of auditory, visual and somatomotor environmental stimuli. This is based on conditional allocation of awareness to competing stimuli in the environment (Petrides, 2005). Thus, the learned conditional rules provide a mechanism by which attention can be flexibly switched between multiple stimuli or responses in a situation given under different conditions. There is also strong evidence that lesions of the rostral part of the lateral cortex damage selectively visuo-motor conditional tasks (Petrides, 2019). In contrast with the caudal region, the mid-dorsolateral prefrontal cortex is involved in performance of working memory that requires the monitoring of specific subsets of information from a collection of stimuli (auditory, visual and somatomotor). Research shows that the fundamental problem of working memory tasks lies within the complex monitoring requirements of the task itself (Petrides, 2000). Thus, the lateral prefrontal cortex plays an essential role in the distinguishing of auditory, visual and somatomotor stimuli and giving those stimuli a meaningful value for further processes as value-based learning.

Together with the caudal-rostral axis that was described above, there is also a dorsal-ventral

axis organization within the lateral prefrontal cortex. This mid-dorsolateral prefrontal cortex is a region specialized in the process of mentalizing events that are firstly interpreted as constant and maintained, but can later be re-coded in abstract form for the purpose of predicting expected events (Petrides, 1996). This is not to maintain information for short-periods of time, but for a conscious active control of planned cognition and behaviour. So, according to Petrides (1996), those specific functional contributions of the mid-dorsolateral prefrontal cortex make some aspects of planning and organization of behaviour possible.

Due to anatomical studies, we know that the mid-dorsolateral prefrontal cortex has rare access to the hippocampal region through the retrosplenial cortex (Morris, Pandya, et al., 1999; Morris, Petrides, et al., 1999). This fibre system that connects the hippocampal region with the mid-dorsolateral prefrontal cortex is in all likelihood the anatomical connection which the mid-dorsolateral prefrontal cortex uses in order to affect working memory (Petrides, 2005). In addition, the right mid-ventrolateral prefrontal cortex was found to be involved in active memory retrieval (Kostopoulos & Petrides, 2003) as well as the verbal episodic and semantic retrieval of memory (Poldrack et al., 1999).

In conclusion, the lateral prefrontal cortex contributes to the following processes: it distinguishes the optimal course of action by adding value to different choice of options in varying situations. When competing against an influential alternative the lateral prefrontal cortex can represent beneficial choice options, and it engages cognitive control by representing value and representing value of conceptual beliefs (Dixon & Christoff, 2014).

The medial prefrontal cortex

There is a wide variety of studies known to explain the role of the medial prefrontal cortex. This field is covered mostly by studies on decision making, which includes conflict monitoring (Botvinick et al., 2004), reward-guided learning (Rushworth et al., 2011), executive control (Posner et al., 2007), error identification; which includes the detection of cognitive misses as a result of conflicting monitoring (Holroyd et al., 2002) and deciding about risk and reward (Bechara & Damasio, 2005). Because of its particular selective involvement in the retrieval of remote memories, the medial prefrontal cortex also plays a key role in memory (Frankland et al., 2004; Takashima et al., 2006). This can be seen as the long-term memory, because the memory spanning is up to hours or longer. But, an association with short term memory has also been found. Rats with lesions in the medial prefrontal cortex have problems recalling rewards associations over a 30 minutes delay (Seamans et al., 1995) or waiting for a cue to respond in 30 seconds (Narayanan & Laubach, 2006). Thus, evidence has shown that the medial prefrontal cortex plays an essential role in the recent, remote and short-term memory (Euston et al., 2012b).

The most consistent outcome of research regarding the medial prefrontal cortex is the strong modulation by motivationally prominent events, positive as well as the negative events (Euston et al., 2012b).

In addition, the medial prefrontal cortex is also one of the major recipients of pathways from the amygdala and has a projection to the striatum (Ghashghaei et al., 2007). The ventral medial prefrontal cortex has a strong connection with the anterior insular areas, known to be involved in pain perception (Jasmin et al., 2004) as well as in interoception (Allen et al., 1991). The amygdala innervates the prefrontal region, suited at the posterior part of the medial prefrontal cortex, also known as the cingulate cortex. The medial prefrontal cortex is therefore known as a key structure in the mentalizing network. A big part of the mental self, the self-representation, is known to be organized by the medial prefrontal cortex. Whereas the dorsomedial prefrontal cortex, the upper region, has an important role in the evaluation of information about oneself (Watanabe, 2017). Neuroimaging studies have shown that the medial prefrontal cortex is typically involved in the

default network when processing social and self-related information. The default network is preferentially active when the individual is not focused on an external environment (Buckner et al., 2008). The default mode network is formed together with the posterior cingulate cortex, the posterior parietal lobe, the lateral temporal cortex and the hippocampal formation (Buckner et al., 2008).

Analysing the functionality of the rodent prefrontal cortex

With the understanding of the general functionality of the prefrontal cortex as described above, it is of great interest to further analyse the functionality within these regions. With rodents being the leading model organisms for biomedical research for over a century, they are a well-established source of information for the neurosciences (Ellenbroek & Youn, 2016). Experimental animal studies provide new potential insights into an array of brain mechanisms, such as detailed interactions of classical and novel neurotransmitters and neurodevelopmental mechanisms. Those animal models are of great importance as a tool for the study of the understanding of the brain (Van den Buuse et al., 2005). An important new tool for neuroscience is the technique called optogenetics, allowing the detection of complicated connectivity in the brain and on-demand direct manipulation of specific neuronal pathways (Kale et al., 2015). This technique has generated considerable excitement in the field of neuroscience (Lalumiere, 2011). Optogenetics make use of the combination of tissue- and cell type specific expression of microbial proteins that are sensitive to light, which are called the opsins. Together with precocious optical methods and the control of the activity of specific cell-populations in vitro as well as in living animals, this method leads to high temporal precision and even reversibility (Boyden et al., 2005; Nagel et al., 2003). This provides new means for establishing a causal relationships between complex behaviours and neuronal activity (Belzung et al., 2014).

With this in mind I will look into this new kind of research to explore new insights in the rodent literature on the connectivity and functionality of the prefrontal cortex. Knowing how the prefrontal cortex and its components are involved in cognitive processes like processing sensory input and decision making, I will explore these cognitive processes in interesting complex phenomena like stress and learning.

Stress

The recent development of the optogenetic tool has provided a new opportunity to investigate the neural circuits playing a role in stress by manipulating selected neuronal systems (Deisseroth, 2012). Within the research of the neurobiology of depression and stress, optogenetics have given some new interesting insights. Areas as the medial prefrontal cortex and the anterior cingulate cortex, as mentioned earlier, are associated with social cognition. Social cognition is a complex social process that requires the integration of a collection of behaviours like saliency detection, reward-seeking, knowledge of oneself and others, motivation and the possibility of flexibly adjusting behaviour in social groups (Bicks et al., 2015). Three key behaviours that are essential for normal social processing are social motivation, social recognition and a dominance hierarchy. These three key behaviours which also includes domains as fear and anxiety are essential for rodents as well as for humans (Bicks et al., 2015). Therefore rodents are a valuable model organism.

The experiments using optogenetics which focused mainly on the dopaminergic system, specifically the dopaminergic cells within the Ventral Tegmental Area (VTA) (which receives glutaminergic afferent signal from the prefrontal cortex) have found the following results. Photo-stimulation with optogenetics of these VTA cells reduced depressive-like behaviours in mice that were exposed to chronic stress which created a depressive phenotype, while suppression had the opposite effect (Tye et al., 2013). Which is interesting, because another experiment which stimulated the same VTA dopaminergic neurons revealed the opposite pattern, stimulation of the VTA neurons

elicited depression-like symptoms in mice (Chaudhury et al., 2013). Nevertheless, there was a difference, where the first experiment made use of chronic stress, the second one used social defeat, which consisted out of two sessions of social defeat on the same day. As seen later on, the stimulation of the VTA-nucleus accumbens projection was adequate enough to create depression-like phenotypes (Chaudhury et al., 2013). Where inhibition of the medial-prefrontal cortex VTA-projections provoked depression-like effects (Belzung et al., 2014).

Another way to investigate stress-like phenotypes, is to look at an altered functional activity within the medial regions of the prefrontal cortex instead of photo-stimulating specific areas. Because studies of the depressed brain suggested that decreases as well as increases in cortical activity could lead to depression-like symptoms (Fales et al., 2008). Rodents exposed to stress can undergo a modification of the activity and the morphological profile of neurons within the medial prefrontal cortex (Cook & Wellman, 2004; Dias-Ferreira et al., 2009). Long lasting decrease in functional activity of the ventral area of the medial prefrontal cortex was followed by short periods of social defeat stress (Covington et al., 2005). According to the experiment in mice of Covington et al., (2010) the stimulation of the medial prefrontal cortex has an antidepressant-like response, including the restoration of social interaction. The activation of the medial prefrontal cortex immediately leads to changes in brain circuits that correct behavioural shortfalls. This circuit contains the ventral hippocampus, the medial prefrontal cortex and the basolateral amygdala, a highly conserved network that supports anxiety behaviour in an interdependent manner (Lesting et al., 2013; Sierra-Mercado et al., 2011). According to yet another research which highlights the optogenetic approach, there is demonstrated that the direct pathway between the ventral hippocampus and the prefrontal cortex is necessary for anxiety-like behaviour (Padilla-Coreano et al., 2016). Padilla-Coreano et al., (2016) suggested that optogenetic inactivating one of the three circuits (ventral hippocampus, medial prefrontal cortex or the basolateral amygdala) alters avoidance and anxiety behaviour. And indeed, inhibition of the terminals within the ventral hippocampus disturbed the synchrony between the ventral hippocampus and the medial prefrontal cortex, which inhibited the exploration-behaviour in rodents as a result. This is in agreement with other research that suggested that silencing any of those three structures alters avoidance behaviour (Shah & Treit, 2003). In comparison with similar research, where by optogenetically inhibiting the basolateral inputs to the ventral hippocampus or the medial prefrontal cortex, anxiety and avoidance behaviour was altered (Felix-Ortiz et al., 2016; Felix-Ortiz et al., 2013). This underlines the great connectivity between those three regions and the role they play in stress-related behaviour like avoidance and anxiety.

Another notable findings by an optogenetic approach, is that the dorsal medial prefrontal cortex plays a significant role in food seeking in rodents. Rats induced with yohimbine, a pharmacological stressor which generates stress-like states (Calu et al., 2013) decreased their food seeking behaviour when the dorsal medial prefrontal cortex was inhibited by means of optogenetic tools (Josselyn, 2010).

What seems to be very important to consider is the way that stress is quantified as a construct. This difference in quantification could have led to this sometimes seemingly contradicting set of results.

Memory

With the knowledge that the behavioural output which comes from stress can be altered by optogenetics, and knowingly that a memory is thought to be encoded by a scarce set of neurons (Binder et al., 2019), I will examine the question if a specific memory can provoke a behavioural output by activating a subset of neurons with optogenetics. We know from the literature considered so far that the prefrontal cortex has strong connections with memory. The orbitofrontal prefrontal

cortex has a connection with the hippocampus through the posterior cingulate cortex by the dorsal route through the entorhinal cortex. The mid-dorsolateral prefrontal cortex with the hippocampus through the retrosplenial cortex, which connects it with active memory retrieval. And as a result of the particular selective involvement in the retrieval of remote memories, the medial prefrontal cortex also plays a key role in memory.

The two-stage theory of memory formation states that memory footprints are initially encoded into the hippocampus. The hippocampus serves as a short-term storage site, and are then, in the development of memory consolidation, transferred to the neocortex for long-term memory (Cenquizca & Swanson, 2007). The monosynaptic projections of the ventral and the intermediate hippocampus to the pre-, and infralimbic regions of the medial prefrontal cortex have already been found (Rasch & Born, 2013). This form of memory consolidation benefits from sleep, particularly from the oscillatory rhythms resulting from deep non-rapid eye movement sleep, the neocortical slow oscillations, the thalamus-cortical spindles and the hippocampal sharp-wave ripples (SPWRs) (Chauvette et al., 2012). Neocortical slow oscillations can induce long term plasticity-like mechanisms (Binder et al., 2014) and the improvement of those neocortical slow waves has led to improved consolidation of memory in rats (Peyrache et al., 2009). Research showed that neuronal repetition in the medial prefrontal cortex appears preferentially during the hippocampal sharp-wave ripples episodes during sleep which improves memory consolidation (Baddeley, 1992). According to the research of Binder et al., (2019) optogenetic inhibition of the axonal terminals of the hippocampal projections within the medial prefrontal cortex in slow-wave sleep did impair recent memory performance in mice. Furthermore, this inhibition interrupted the development of choosing the most efficient search strategies in the Barnes maze test. This indicates that the projections from the hippocampus to the medial prefrontal cortex have a considerable contribution to sleep-dependent memory consolidation.

In addition to the consolidation of memory, the working memory is also an interesting and important part of the memory-concept. The working memory of the brain is a complex process that refers to the brief storage of information which is necessary for cognitive performance (Kim et al., 2013). The working memory involves the storage of information in a time scale of seconds to minutes which is necessary for cognitive performance. The working memory is considered to represent memory of two different sensory stimuli that are separated by a delay. This delay needs a form of time-tracking or memory in which the medial prefrontal cortex is involved (Gilmartin & Helmstetter, 2010). The medial prefrontal cortex has been involved in this process of working memory performance as it has found that reversible pharmacological inactivation of the medial prefrontal cortex impaired working memory performance (Gilmartin & McEchron, 2005). Nonetheless, causal evidence for the essential role of the medial prefrontal cortex has only recently been provided using optogenetic intervention. The functionality of the working memory performance can be determined using a trace fear-conditioning tasks, in which a conditioned stimulus is followed by an unpleasant unconditioned stimulus after a delay of a few seconds. In this delay of a few seconds, the prefrontal neurons are known to display a constant firing (Gilmartin et al., 2013), which implies a role for the prefrontal cortex in maintaining a representation of the conditioned stimulus during the delay. Optogenetic inhibition of the prefrontal neurons during this delay phase of the trace fear-condition, impaired learning of an association between the conditioned and the unconditioned stimulus (Courtin et al., 2013) which was the first evidence for the involvement of the prefrontal cortex with working memory as a result of optogenetic tools.

Specific roles for the subareas of the prefrontal cortex have been established in the definition of conditioned fear memory, with dorsal regions intervening the encoding and expression of fear memory and ventral regions contributing to the consolidation and expression of faded memory (Quirk et al., 2003).

With the newly developed knowledge how the brain is involved in the formation and consolidation of memory by optogenetic tools together with the support of optogenetic studies which report that neuronal assemblages engaged during the acquisition of memory continue to support context-specific memories, a new kind of experiments could be set up. These findings led to experiments that demonstrated that optogenetic activation of the original cell assembly can induce expression of the context memory (Liu et al., 2012a; Ramirez et al., 2013), while rapid inactivation by inhibition has led to memory loss in rodents (Goshen et al., 2011). So interestingly, it is possible not only to alter behaviour as a result of optogenetics and neurophysiology, but to activate subsets of behaviour as well. I will highlight this in the following section by the use of a subset of experiments.

Nevertheless, to prove that a specific cell population is the cellular basis of a specific memory engram, a mimicry experiment has to be conducted to prove that the direct activation of that population is sufficient enough for inducing the associated behavioural output. (Gerber et al., 2004). As already mentioned earlier, the hippocampus is thought of being a key linkage in the formation of the contextual component of memories, followed by the neocortex. Modelling (Treves & Rolls, 1994) as well as experimental studies (Nakashiba et al., 2012) have established a critical role of the dentate gyrus of the hippocampus in the discrimination of similar contexts. Research has shown that early gene expression in cellular studies showed a scarce population of dentate gyrus granule cells that were activated in given contexts (Schmidt et al., 2012). Furthermore, as the same population of the dentate gyrus granule cells are activated frequently in the same environment, different environments or different tasks activate different subsets of dentate gyrus granule cells (Chawla et al., 2005; Satvat et al., 2011). These findings above made the dentate gyrus granule cells an ideal target for the formation of contextual memory engrams that could represent various environments. When an active population of hippocampal dentate gyrus neurons were labelled during fear learning by Xu Liu et al., (2012) and later optogenetically reactivated, the mice showed increased freezing behaviour, associated with fear-like phenotypes. Reactivation of cells labelled in a context not associated with fear did not elicit freezing in mice that were previously conditioned with fear in a different context. This suggests that light-induced fear memory recall is of context-specificity. Those findings induce that activating a few but specific population of hippocampal neurons that contribute to a memory engram could be sufficient enough for the recall of that memory and its behavioural output (Liu et al., 2012a).

In another study, an optogenetic approach was developed that allowed the researchers to manipulate the activity of the dentate gyrus ensembles that were activated during fear memory encoding in infant mice, to test whether the reactivation of those neurons lead to the recovery of those memories in adulthood (Guskjolen et al., 2018). They made use of the concept that high postnatal levels of hippocampal neurogenesis contributes to the accelerated forgetting in infant mice (Akers et al., 2014). Suppressing hippocampal neurogenesis in infant mice slowed the process of forgetting contextual fear memories, which suggests that there is a causal relationship between neurogenesis-mediated remodelling of hippocampal circuits and forgetting during infancy (Akers et al., 2014). The method of contextual fear conditioning is used, because it produces a contextual fear memory that lasts for approximately 24 hours and is then quickly forgotten in infant mice (Akers et al., 2012). Optogenetic stimulation of the dentate gyrus neurons that were tagged during encoding of this contextual fear memory in infants was sufficient enough to induce fear memory recall in adulthood by displaying freezing behaviour.

Evidence from another research has shown that there even can be created a sense of false memory in mice by optogenetic tools. Ramirez et al., (2013) also used fear conditioning in mice as a model for episodic memory. In this research they also used granule dentate gyrus cells that were identified as contextual memory-engram cells. They studied if by artificially activating a previously formed contextual memory engram while delivering foot shocks at the same time can result in the

creation of a false fear memory for the context in which the foot shocks were never administered. And indeed. First, mice were exposed to a specific context, a context where mice were fear-conditioned by seeing a light and receiving a food-shock. By the exposure to this particular context, the granule dentate gyrus cells that where marked, were the cells that were bearing the newly formed fear-memory engram (Ramirez et al., 2013). When those cells where later optogenetically reactivated in a different context, a context where the freezing behaviour (as a result of fear for the shock) was extinguished, but the other factors remained the same, freezing behaviour increased significant. Thus, cells activated previously in the hippocampal dentate gyrus can subsequently serve as a functional *conditioned stimulus* in a fear-conditioning context when artificially reactivated during the delivery of an unconditioned stimulus. The consequence, stated by the Ramirez et al., (2013) is that there is a formation of a false associative fear memory to a conditioned stimulus that was not available at the time that the unconditioned stimulus was delivered. This thus further supports that memory recall can be induced for a certain fear memory by optogenetically reactivating the corresponding engram in the dentate gyrus (Doyère & Laroche, 1992; Liu et al., 2012b).

Discussion:

The prefrontal cortex is responsible for the sensory information processing of multiple cognitive functions as for example the processing of sensory information and perception (Goyal et al., 2008). The prefrontal cortex can be subdivided in three major regions: the orbital prefrontal cortex, the medial prefrontal cortex and the lateral prefrontal cortex.

The orbital prefrontal cortex represents the value of stimuli, it makes sense out of 'what' the representation is for the sensory systems such as taste, olfaction, visual, auditory and somatosensory information system (Rolls., 2019a). Thus, the orbital prefrontal cortex plays a key role in the rating of a reward based on the sensory input. The orbital prefrontal cortex only represent the value, it is not responsible for the actions. This is due to the projections to the other areas such as the autonomic functions as the hypothalamus, midbrain and the insula (Critchley & Harrison, 2013). The orbital prefrontal cortex is also connected to memory. The orbitofrontal cortex has strong connections with the posterior cingulate cortex, which has strong connections to the hippocampus trough the entorhinal cortex. This could probably be the connection that gives meaning to memories based on sensory input. The reward- and non-reward routes can operate through the basal ganglia routes: the striatum, ventral pallidum and the globus pallidus routes. They influence the lateral habenula, which in its turn can influence the dopamine neurons in the substantia nigra due to the GABAergic rostro-medial tegmental nucleus. This provides the reward, non-reward and a reward prediction error signal (Haber, 2014; Proulx et al., 2014).

The lateral prefrontal cortex plays an important role in the complex system of value-based learning and decision making (Dixon & Christoff, 2014). Strong evidence has shown that the rostral-caudal axis of the functional organization involved in those processes lies within the lateral prefrontal cortex (Petrides, 2005). The caudal dorsolateral prefrontal cortex has a critical role in the selection between different aspects of auditory, visual and somatomotor environmental stimuli. The mid-dorsolateral prefrontal cortex is involved in the performance of working memory that requires monitoring of distinctions of information. Thus, the lateral prefrontal cortex plays an essential role in the distinguishing of auditory, visual and somatomotor stimuli and giving those processed stimuli a meaningful value for further processes such as value-based learning. Furthermore, the lateral prefrontal cortex is also involved in memory, just as the orbital prefrontal cortex, also through connections with the hippocampus, but the lateral prefrontal cortex has this connection via the retrosplenial cortex. Therefore, as a result of research, the right ventral part of the lateral prefrontal cortex has been associated with memory retrieval (Kostopoulos & Petrides, 2003), the mid-ventrolateral prefrontal cortex with verbal episodic and semantic retrieval (Poldrack et al., 1999). In

conclusion, the lateral prefrontal cortex contributes to processes as the distinguishing of the optimal course of action by adding value to different choice of options in varying situations regarding on the auditory, visual and somatomotor environmental stimuli. And, when competing against an influential alternative, the lateral prefrontal cortex can represent beneficial choice options (Dixon & Christoff, 2014).

The medial prefrontal cortex contains a wide variety of studies to explain its role. This field is mostly covered by studies on decision making and memory. Because of its particular selective involvement in the retrieval of remote memories, the medial prefrontal cortex plays a key role in memory (Frankland et al., 2004; Takashima et al., 2006). Long term memory (up to hours or longer) as well as short-term memory (seconds to minutes) have both been associated with the medial prefrontal cortex (Easton et al., 2012b). In addition, the medial prefrontal cortex is one of the major recipients of pathways from the amygdala and has a known projection to the striatum (Ghashgaei et al., 2007). The ventral part of the medial prefrontal cortex has a strong connections with the anterior insular areas, known to be involved with pain perception (Jasmin et al., 2004) as well as interoception (Allen et al., 1991). The amygdala innervates the prefrontal region, suited at the posterior part of the medial prefrontal cortex, this area is also known as the cingulate cortex. Because of this high connectivity, the medial prefrontal cortex is therefore also known as a key structure in the mentalizing network. A big part of the mental self, the self-representation, is known to be organized by the medial prefrontal cortex, whereas the dorsomedial prefrontal cortex has an important role in the evaluation of information about oneself (Watanabe, 2017). According to neuroimaging studies, the medial prefrontal cortex is also involved in the default network. A network that is preferentially active when an individual is not focused on an external environment and processes social and self-related information. This network consists out of the posterior cingulate cortex, the posterior parietal lobe, the lateral temporal cortex and the hippocampal area and the medial prefrontal cortex (Buckner et al., 2008).

Thus, the prefrontal cortex is involved in a lot of cognitive processes. This understanding about the general functionality on the prefrontal cortex based upon the anatomical analysis gave the opportunity to further analyse the functionality within the discussed regions of the prefrontal cortex. In this review, the rodent model and the technique of optogenetics are highlighted in phenomena like stress and memory.

Areas as the medial prefrontal cortex and the anterior cingulate cortex are associated with social cognition. When the ventral tegmental area (VTA), which receives glutaminergic afferent signals from the prefrontal cortex, is optogenetically manipulated, some new interesting results followed. Stimulation of those VTA cells reduced depressive-like behaviour in mice that were exposed to chronic stress, while suppression had the opposite effect (Tye et al., 2013). But, stimulation of those same VTA cells in another experiment elicited depression-like symptoms in mice (Chaudhury et al., 2013). The substantial difference between these two experiments is the way stress is quantified as a construct. Tye et al., (2013) made use of the chronic stress-model, where Chaudhury et al., (2013) used the social defeat. Which was not chronic, but the procedure consisted out of two sessions of social defeat on the same day. As seen later on, the stimulation of the VTA-nucleus accumbens projection was adequate enough to create a depression-like phenotype. Where inhibition of the medial prefrontal cortex VTA projections provoked depressive-like effects (Belzung et al., 2014). Another perspective to investigate stress-like behavioural phenotypes, is the one where there is looked at altered functional activity within the whole medial prefrontal cortex instead of the specific subset of VTA neurons. This showed that long lasting decrease in functional activity of the ventromedial prefrontal cortex was followed by short periods of social defeat (Covington et al., 2005). Optogenetic stimulation of the medial prefrontal cortex has had an antidepressant-like response, including the restoration of social interaction (Covington et al., 2010). On behalf of the

optogenetic approach, the direct pathway between the ventral hippocampus and the prefrontal cortex seemed to be necessary for anxiety-like behaviour (Padilla-Coreano et al., 2016). The inhibition of the terminals within the ventral hippocampus of rodents disturbed the synchrony between the hippocampus and the medial prefrontal cortex, which as a result inhibited exploration-behaviour. And, when the dorsomedial prefrontal cortex in rodents was inhibited optogenetically in stress induced mice as a result of the pharmacological stressor yohimbine, food seeking behaviour decreased (Calu et al., 2013).

Thus, the behavioural output concerning the phenomenon stress can indeed be manipulated by optogenetic tools. But what seems to be very important to take in consideration is the way stress is quantified as a construct in experiments. This difference in quantification of the construct stress could lead to the sometimes seemingly contradicting results within research.

With the knowledge that the behavioural output which comes from stress can indeed be altered by optogenetics and that the prefrontal cortex has strong connections with memory, this review furthers aimed to examine if a specific memory can provoke a behavioural output by optogenetically activating a subset of neurons.

The monosynaptic projections of the ventral and intermediate hippocampus to the pre-, and infralimbic regions of the medial prefrontal cortex have already been found (Rasch & Born, 2013). Optogenetic inhibition of the hippocampal axonal terminals within the medial prefrontal cortex in slow-wave sleep impaired recent memory performance and consolidation in mice. It also interrupted the development of choosing the most efficient search strategies in the Barnes maze test. In addition to the consolidation of memory, the working memory is also highly associated with the prefrontal cortex. The functionality of the working memory performance can be determined using a trace fear-conditioning task, in which a conditioned stimulus is followed by an unpleasant unconditioned stimulus after a delay of a few seconds. In this delay, prefrontal cortex neurons are known to display a constant firing (Gilmartin et al,. 2013). Optogenetic inhibition of those same prefrontal cortex neurons during this delay impaired learning of an association between the conditioned and the unconditioned stimulus, which was the first optogenetic evidence of the involvement of the prefrontal cortex with working memory. Interestingly, it seemed not only possible to alter behaviour as a result of optogenetics, but activating subsets of behaviour was possible as well as a result of the optogenetic tool.

When active hippocampal dentate gyrus neurons that were labelled during fear learning, and later optogenetically reactivated, resulted in increased freezing behaviour in mice, associated with fear-like phenotypes (Xu Liu et al., 2012). And, the optogenetic stimulation of the dentate gyrus neurons that were tagged during encoding of contextual fear memory in infant mice was sufficient enough to induce fear memory recall in adulthood by displaying freezing behaviour (Guskjolen et al., 2018). Evidence from another research has shown that there can even be created a sense of false memory in mice by optogenetic tools (Ramirez et al., 2013). Cells which were previously activated in the hippocampal dentate gyrus when associating a fear memory to a context, and later optogenetically reactivated in a neutral context, induced freezing-like behaviour in mice. Thus, memory recall can indeed be induced for a certain fear memory by optogenetically reactivating the corresponding engram in for instance the dentate gyrus.

The results mentioned and described above do indeed, nevertheless partially, explain how cognitive processes and the behavioural responses handled in this review are explained based on the examination of the functionality of the neurophysiology of the prefrontal cortex. The results also showed that subsets of behavioural outputs can be altered and sometimes even induced with optogenetic tools in rodent models. The optogenetic tool and rodent model prove themselves important for the future understanding and examining of the functionality of the neurophysiology of the prefrontal cortex.

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