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Abstract

Decision making plays a major role in everyday life. When making a decision one can be more or less confident about it. Here we show that the level of decision confidence can be a result of forerun success or loss. Furthermore, decision confidence reflects an individual's knowledge about trial outcome and affects the following decisions. The level of decision confidence can predict trial outcome and overall task performance. For this, Long-Evans rats were trained in an auditory two-alternative-choice decision wagering task to assess decision confidence by measuring the time the animal was willing to pay in order to receive reward. With this behavioural paradigm we established a method which allows the examination of neuronal circuits responsible for metacognitive processes. Fundamental for processing incoming information and enabling goal-directed decision making is the so called working memory, forming the basis for many cognitive processes such as those belonging to metacognition. We could demonstrate that the medial prefrontal cortex is crucial for working memory by silencing this area using muscimol injections. Disabling the function of working memory caused a tremendous loss in performance during a working memory-guided decision making task.

Zusammenfassung

Entscheidungen zu treffen ist ein essenzieller Bestandteil des alltäglichen Lebens. Das Vertrauen in eine getroffene Entscheidung spielt dabei eine wichtige Rolle. Im Zuge dieser Arbeit konnten wir zeigen, dass das Ausmaß an Vertrauen in eine getroffene Entscheidung meist aus bereits vorangegangenen Erfahrungen resultiert, welche erfolgreich oder mit einer Niederlage ausgegangen sein können. Das Ausmaß an Vertrauen in eine Entscheidung scheint das innere Wissen, eine Vermutung über den Ausgang dieser Entscheidung, zu reflektieren. Wir konnten des Weiteren zeigen, dass das angegebene Ausmaß an Vertrauen eines Individuums, eine Vorhersage über den Ausgang einer einzelnen Entscheidung darstellen kann. Die Summe aller Selbsteinschätzungen lässt uns auf die Leistung des Tieres über den gesamten Task hinweg schließen. Um diese Beobachtungen zu ermöglichen, wurden Long-Evans-Ratten in einem auditiven „two-alternative-choice decision wagering task" trainiert. In diesem Task hatten die Tiere die Aufgabe, die Richtigkeit ihrer Entscheidung abzuschätzen und anzuzeigen, wie lange sie bereit sind auf ihre Belohnung zu warten. Je länger eine Ratte wartet, desto höher wird ihr Vertrauen in diese Entscheidung gewertet. Mit Hilfe dieses Bezugssystems haben wir eine Methode etabliert, welche ermöglichen soll, die neuronalen Netzwerke besser zu verstehen, welche für diesen metakognitiven Prozess zuständig sind.
Eine ganz grundlegende Funktion in der Verarbeitung von sensorischer Information hat das Kurzzeitgedächtnis (working memory) des Gehirns inne. Es ermöglicht Entscheidungen zielgerecht zu treffen und legt damit den Grundstein für metakognitive Vorgänge, wie dem Vertrauen in getroffene Entscheidungen. Mittels Muscimol-Injektionen in den medialen präfrontalen Cortex von Ratten, welche die dortige neuronale Aktivität vollständig hemmten, konnten wir die Bedeutsamkeit dieser Hirnregion für das Kurzzeitgedächtnis (working memory) dokumentieren. Das Ausschalten des Kurzzeitgedächtnisses (working memory) verursacht eine erhebliche Verschlechterung in der Ausführung der erlernten Problemlösung.

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I.
Mammalian Auditory Perception

Compared to visual perception, investigation on the auditory system was left behind for a long time. People found it difficult to understand auditory perception since they couldn't find *optimal stimuli*, like oriented bars for the visual system (Hubel and Wiesel, 1962). No optimal stimuli have yet been found for auditory perception (Hromadka and Zador, 2009). Obviously audition is a very important sense for mammalian species. Depending on the animal's habitat, evolution brought about a number of different cochlear specialisations (e.g. small animals are sensitive to higher frequencies than bigger animals) optimising the mammal's auditory perception. Nonetheless mammalian central auditory pathways are very similar, making rodents and primates good investigation models (King et al., 2015). Due to neuronal activity properties the auditory system in mammals seems to be very suitable to investigate excitatory and inhibitory mechanisms in functional neuronal networks (King et al., 2015).
From behavioural experiments we know that animals do not always show a clear reaction to an auditory stimulus. But that doesn't automatically mean the brain didn't perceive a stimulus. There are many factors contributing to if and how auditory stimuli are perceived in a cognitive way, or if they are leading to a representation in a certain brain area (DeWeese et al., 2005). From behavioural perspective, reasons for a missing reaction can be a lack of motivation or no information downstream to motor control (Deweese and Zador, 2005). Yet, in physiological studies neurons of the primary auditory cortex act very unstable, show variable firing patterns and appear to be greatly flexible (Hromadka and Zador, 2007).

I.1. Stimulus Processing and Masking

An auditory stimulus travels from the cochleo-vestibular nerve through the brain stem and passes the inferior colliculus in the mesencephalon. After being processed in the thalamus the stimulus arrives in the primary auditory cortex (King et al., 2015).
The basilar membrane of the cochlea represents a frequency map. It is stiffest and most narrow at the basement and most flexible and widest at its apex. Due to these textual properties, tones of high frequencies provoke hair-cells at the apex and tones of lower frequencies stimulate cells around the basement. A representation of *critical bands* has been found along the basilar membrane of the rat auditory system with a width of approximately 1mm. A critical band is fenced by a certain higher and a lower frequency into which a tone can fall. Tones that fall into the same critical band will stimulate the same locus on the basilar laminar of the inner ear. If stimuli appear to be within the same critical band they are heard as one single tone. This phenomenon is called *masking* (King et al., 2015).
Spiral ganglion cells and auditory nerve fibres act as filters. They filter sound for intensities bigger than 30 dB SPL (sound pressure level) above the tone response threshold. The subcortical inferior colliculus is filtering as well. The central nucleus of the inferior colliculus receives inputs from the lower auditory brainstem nuclei. Sound representations in the lower nuclei are transmitted to the central nucleus and separated to major and minor frequency gradients. The ventromedial area of the central nucleus of the inferior colliculus has neurons sensitive to high frequencies. In the dorsolateral area sit neurons specific to lower frequencies (King et al., 2015).

I.2. Auditory Cortex and Critical Bands

Critical bands are frequency dependent, meaning that bandwidth increases with critical band centre frequency. However, they are independent of sound intensity. Humans have sharper critical bands as indicated by the fact that non-human species show larger *critical ratios* than humans. A critical ratio

of two distinct tones is the minimum difference in frequency needed to be able to differentiate those two. The reason why rodents might have problems to detect a tone in a noisy background may be the fact that they have larger critical ratios (Yost and Shofner, 2009). Thus, humans have better frequency selectivity than other species (King et al., 2015). Neurons that represent critical bands are found in the central and ventral primary auditory cortex, whereas neurons in the dorsal primary auditory cortex are involved in discriminating sound sources. Compared to critical bands, neural responses in the primary auditory cortex are not dependent on specific frequencies, but intensities (neuronal power-spectrum) (King et al., 2015).
In rat, cat and mouse auditory cortex excitation and inhibition are balanced. Hence, the neuronal excitation by a tone is in its magnitude proportional to the GABAergic inhibitory response. This balanced auditory excitation/inhibition is not found in young animals but has to be acquired during development (King et al., 2015). The rodent auditory cortex is the most plastic cortical region during early postnatal phase, beginning at day P 10. In the first month, bandwidth, spatial sound localisation and the excitatory-inhibitory balance develop. Interestingly, lactating mother mice show a higher activity of parvalbumin expressing interneurons sensitive to higher frequencies, which fits to the ultrasonic vocalisation of pups (Cohen and Mizrahi, 2015).

I.3. Complexity of the auditory cortex

The auditory nerve contains far less neurons than the auditory cortex. Each cochlea covers approximately 16 000 sensory hair cells, the primary auditory cortex enfolds at least ten thousand times more neurons. Why is auditory information transformed from more simple units into highly complex fields? There are some possible suggestions: The mass of extra neurons is needed to overcome cortical noise. Particularly, neurons of the same cortical column may pass on information downstream to create an average of the processed sensory input in order to get a “read out”. Another explanation would be that additional neurons could provide context-dependent information to make computation easier. The third possibility would be that the auditory cortex combines bottom-up sensory signals coming from the auditory nerve with top-down inputs from cortical fields deriving from goals, expectations and attention (DeWeese et al., 2005).

I.4. Attention and its effect on neuronal activity in the primary auditory cortex

The state of attention of an individual plays a crucial role for neuronal activity in the auditory cortex. In humans, electroencephalogram-recordings revealed that neuronal response in the auditory cortex was enhanced during trials when the subject focused on the stimulus compared to trials of attentional withdrawal (Picton et al., 1971). Studies on cats showed that attention towards a stimulus lead to increased electrophysiological activity in the auditory cortex (Hernandez-Peon et al., 1956). In rat auditory cortex 15% of neurons show modulated activity depending on the task requiring auditory or olfactory attention. To conclude, neuronal response to auditory stimuli not only depend on the acoustic properties, but also on the attentional state of mind (Hromadka and Zador, 2007).

I.5. Firing patterns in auditory cortex and neuronal reliability

It has been shown, that the awake auditory cortex differs strongly from the anesthetised one. In an anesthetised brain neuronal activity is only transient. In awake animals both transient and sustained activity has been recorded. The fact that awake animals show sustained activity suggests the existence of optimal stimuli activating auditory nerves in a more efficient, long-lasting way (Hromadka and Zador, 2009).

Recordings in head-fixed awake rats, using glass electrodes attached to single neurons, show that neuronal activity in the auditory cortex is in general very sparse. Only 5% of the population responds to either simple or complex (natural) stimuli. However, sparse neuronal representation implies several advantages: the information coded by neuronal activity is much clearer, because there are few active neurons. In a computer generated model sparse stimulus representation is simulated by a log-normal-distribution. Such distributions are characterised by a few cells with much higher activity. It is very likely that these neurons are crucial for stimulus discrimination (Hromadka and Zador, 2009).

Neurons in the auditory cortex act in a very unstable and highly variable fashion. Across trials neuronal responses to specific stimuli are variable. Also the number of spikes generated by a neuron varies from trial to trial and therefore cannot contribute to a useful estimation of the stimulus type. It seems that spike trains of auditory neurons follow a random Poisson process (DeWeese et al., 2005).

Alternatively, at each time point the cortex is in a different state or performing a different computation from one trial to the next. This would be in line with the assumption that the cortex is highly flexible. High neuronal variability per se does not mean that information important for the individual is lost or not processed (DeWeese et al., 2005).

Neuronal reliability depends on firing rate (spike count-reliability) and timing of action potential firing (spike-timing reliability). Spike-count reliability is assessed by counting the number of spikes produced by a neuron as a response to a particular stimulus in a certain time window. The timing describes the time point the neuron spikes due to the onset of a stimulus.

When looking at timing reliability, spiking as a response to an auditory stimulus can be temporally very precise in the cortex. The most reliable spikes in auditory cortex exhibit a jitter of less than 1 ms while in the visual cortex it would be at least 5 ms. Conversely, the timing of spiking after a stimulus onset is quite random. Considerably, next to the stimulus specific activity an internal clock might exist in the absence of stimuli like theta or gamma rhythms that may be used as a timing reference (DeWeese et al., 2005).

In terms of firing activity, neurons in the auditory cortex display either binary or Poisson distributed patterns. Both ways of firing can be carried out by one and the same neuron depending on the stimulus and its context. Both rate and temporal coding are necessary for auditory perception (DeWeese et al., 2005).

There are two distinct parameters of neuronal responses to auditory stimuli: Magnitude and *jitter* of neuronal activity. Jitter is the time that passes between a reference point, e.g. the termination of a stimulus, and neuronal spiking. So-called stimulus-locked spikes can have jitter less than 1 ms. Like in a Poisson process some neurons either generate zero or one spike in each trial. This binary response makes further information processing easier (Hromadka and Zador, 2009).

Additionally, it has been described that neurons in the auditory cortex have excitatory or inhibitory actions and that tones, in general, cause brief neuronal excitations followed by inhibition of activity within only a few milliseconds. A reason for this might be that neurons fire only at tone onset to increase temporal precision (Wehr and Zador, 2005). Furthermore, by investigating how inter-click intervals affect the perception of succeeding clicks, it has been shown that for intervals shorter than 128 ms neuronal responses to succeeding clicks were almost entirely diminished in rat auditory cortex (Wehr and Zador, 2005). Interestingly, GABAergic neurons in the auditory cortex showed activity shorter than 100ms (Fritz et al., 2005).

Another phenomenon described for neuronal activity in the auditory cortex that has been mostly investigated in humans is called forward masking. It describes that the first of two stimuli influences the ability of the subject to perceptually detect the second one. If the two stimuli are clicks of same frequency properties, forward masking lasts up to 100 ms. Thus, every second click following after less than 100 ms displays low probability of being detected. In case of two stimuli with different frequency properties the duration of forward masking is drastically reduced to 2-3 ms (Fritz et al., 2005). Notably, thalamic neurons positioned upstream of cortical neurons in the auditory pathway, recover considerably quicker from forward masking than cortical neurons (Wehr and Zador, 2005).

Similar to that, two tones with a high frequency difference, when presented in an alternating rhythm, will be detected as two separated streams. This has been found for auditory perception in humans and monkeys. If the frequencies are too similar, the alternating rhythm appears to be one auditory stream with a galloping character. But if the frequency difference intermediates, sounds will first be detected as galloping stream and then segregates into two different auditory streams. Remarkably, both streams are represented by distinct groups of neuron in the auditory cortex. Single-unit extracellular recordings in the primary auditory cortex of monkeys were able to predict auditory perception of human subjects, which had to differentiate two different tones. In this study by reading the monkeys´ neuronal activity, it was even possible to predict the time span after which an auditory stream would separate into two different streams. Therefore it was possible to record changes in auditory perception for one and the same stimulus within a trial (Deweese and Zador, 2005).

II.
Perceptual Decision Making

II.1. The Posterior Parietal Cortex and its anatomical organisation – An overview of synaptic connections

The rat posterior parietal cortex was observed to be involved in processing sensory information and important for cognitive functions like attention, perception, working and long-term memory as well as spatial learning (Bucci, 2009). In the rat brain, the posterior parietal cortex makes the caudal part of the cortex. It sits between rostral somatosensory regions and the caudal visual areas. The exact location is 3.5 to 5.0 mm posterior to bregma and 1.5 to 5.0 mm lateral from the sagittal midline (Bucci, 2009). Using anterograde and retrograde tracing methods, it was found that in general the parietal cortex gets ipsilateral inputs from medial prefrontal, somatosensory, motor, auditory, lateral visual and retrosplenial cortical regions. Even more general, projecting areas are the medial, lateral, somatic and entorhinal cortex including the claustrum (Wilber et al., 2014). The largest synaptic inputs derive from the dorsal retrosplenial cortex. These projections were significantly stronger than from any other region of the medial network (Wilber et al., 2014). Inputs from primary visual cortex appear to be quite low. Furthermore projections from the medial entorhinal cortex to posterior parietal cortex were generally weak. The parahippocampal cortex gave little direct input to the parietal cortex. Thus it seems that the retrosplenial cortex acts as an interface between parietal cortex and parahippocampus (Wilber et al., 2014). Looking at output connections, the thalamus is projecting ipsilateral from motor, sensory, associative, intralaminar and midline nuclei to parietal cortex. The laterodorsal thalamus is projecting strongly to the posterior parietal cortex, while motor and sensory thalamic nuclei connect more intensively to motor and sensory thalamic regions. The laterodorsal thalamus projects more heavily to the medial parietal cortex. Most motor nuclei project to the lateral parietal cortex (Wilber et al., 2014).
The parietal cortex is connected strongest to the dorsal retrosplenial cortex and shows weaker connectivity to cingulate cortex, temporal cortex, lateral secondary visual cortex and primary visual cortex. The function of the parietal cortex is strongly dependent on dorsal retrosplenial cortex activity (Wilber et al., 2014).
The posterior parietal cortex provides inputs to the postrhinal cortex where projections pass on to the entorhinal cortex and hippocampus. Hence the function of posterior parietal cortex seems to be strongly connected to processes depending on the activity of the medial temporal lobe (Bucci, 2009).
The lateral posterior parietal cortex of the rat has strong reciprocal connections with the retrosplenial cortex. Inputs from the primary visual cortex appear to be quite low (Wilber et al., 2014).

II.2. Perceptual decision making – General concepts and findings

Perceptual decision making is a hierarchical process based on a cascade starting with the encoding of sensory information, followed by accumulation of sensory evidence, computing decision variables and utilisation of decision rules with the final goal to execute a motor response (Bizley et al., 2016).

II.2.1. Priors, decision value, evidence and decision variable

The term *prior*, in decision-based behaviour, is defined by the animal's principal idea how and where to receive a reward by making the correct choice. This idea is formed by the animal's experience, internal value mechanisms and its percept (Gold and Shadlen, 2007).
Evidence for making a decision is based on perceived information about a hypothesis. In a perceptual task neuronal activity is seen as representation of decision evidence.
In a two-alternative-choice task the subject has to accumulate evidence for either hypothesis h1 or

hypothesis h2. The function, describing the probability evidence that can be attained during the decision making process, is P(e|h) (Gold and Shadlen, 2007).
Value is the sum of all benefits and costs each of the decision outcomes can have. Value can easily be manipulated by providing the subject reward. For costs one can imagine wasted time, effort and resources (Gold and Shadlen, 2007).
The *decision variable* is defined by the union of prior, evidence and value, which will be interpreted by the *decision rule* to achieve a choice (Gold and Shadlen, 2007). It is determined by the difference of evidences of two different possible choices. Assuming that a decision is based on the comparison of spike counts of two different neurons, which are most sensitive to one or the other choice, then the decision variable can also be described as the difference in spike counts of two neurons. The decision variable is defined by the subtraction or accumulation of spikes. This process is called integration (Shadlen and Kiani, 2013). The decision variable is developing over time and spans from the very first relevant piece of information to the final choice. The decision rule drives the decision variable and determines when and how the decision variable has reached a certain threshold, leading to a decision (Gold and Shadlen, 2007).

II.2.2. Binary Decision Making – The Signal Detection Theory and Sequential Analysis

Why is the brain willing to deal with noise? Averaging neuronal signals has the benefit of receiving a fast representation of firing rate caused by a stimulus. It seems that cortical neurons have their information in firing rate rather than in total spike number (Shadlen and Kiani, 2013).
Signal detection theory is describing a process to convert noisy perceptual evidence into a categorical choice. The subject is collecting evidence, which is derived from the senses. Evidence can be spike counts of a neuron or a neuronal pool. It is caused by a stimulus or a state, e.g. stimulus present vs. stimulus absent. If collected evidence is informative, its magnitude differs between these two states. Of course evidence is corrupted by noise, which makes it faulty. In binary decisions, as in two-alternative-choice tasks, the decision variable is directly connected to the ratio between the evidence for the two possible choice alternatives P(e|h1)/P(e|h2) (Shadlen and Kiani, 2013). In an example for Signal Detection Theory, one should imagine two neurons, each representing a distinct choice. Both neurons depict a certain likelihood of firing when their specific stimulus is presented. When comparing both of the neurons, the one with the broader firing distribution should influence the animal's decision the most. The overlap of both distributions is noise or error rate. Mathematically, the difference between the two activity pools results in a difference in firing rate. Depending on if the difference is negative or positive, one or the other choice is made (Shadlen and Kiani, 2013).
In the *drift-diffusion model*, evidence, defined by firing rate, is accumulating over time starting in the middle of two possible choices. Each decision has its own threshold. When the threshold is reached, the corresponding decision will be executed. When the accumulation process is terminated before one of the thresholds has been reached, the choice is based on the larger decision value (Shadlen and Kiani, 2013).
Sequential analysis (Gold and Shadlen, 2007) is an extension to the signal detection theory, based on drift-diffusion, and describes the accumulation of evidence over time (Figure 1). It is built on two aspects: The evidence formed by perceived stimuli and the certain threshold which tells whether it is time to stop sampling and committing to a choice. By the sequential analysis the decision variable can be adjusted by each new sample of evidence. A stopping rule could be to sample pieces of evidence until a positive or a negative criterion has been reached (boundaries on the graph). The decision variable evolves in time while decision evidence is momentary (Gold and Shadlen, 2007).

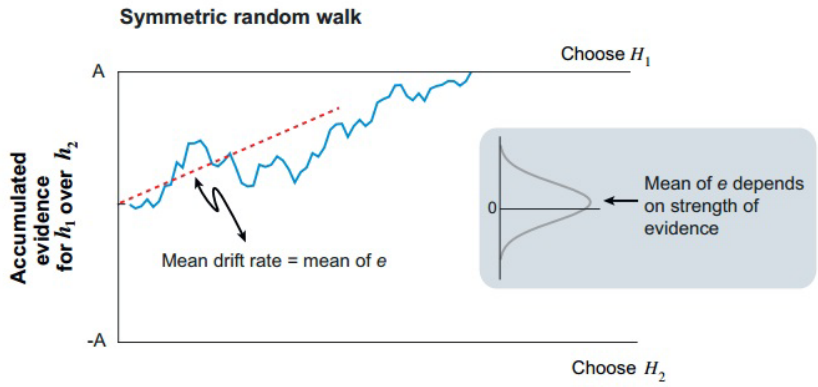

Figure 1, Sequential Analysis, Stopping rule (Gold and Shadlen, 2007)

Several perceptual tasks dealing with binary choices have been introduced to the behavioural field of neuroscience. In those, neuronal recordings led to a better understanding of the decision making process and were supporting signal detection theory as well as the sequential analysis. The two main tasks are described here:
In the vibrotactile frequency discrimination task (Luna et al., 2005; Mountcastle et al., 1990), Rhesus monkeys had to discriminate two tactile vibrations and tell which of the two had higher frequency. Neurons of the primary somatosensory cortex showed a modulation in firing depending on stimulus frequency. Within a trial, neuronal firing rate increased when the high frequent stimulus was presented compared to the stimulus of lower frequency. Order of stimulus presentation was random as well as the exact frequencies (Gold and Shadlen, 2007).
In Random-dot motion direction discrimination task (Shadlen and Newsome, 1996) monkeys had to indicate the moving net direction of dots on a screen by eye saccade to either the left or the right side of the screen, while neurons in medio temporal area and lateral intraparietal area were recorded. In easy trials, where the percentage of dots moving to the same side was high, neuronal firing rate was ramping quicker and higher compared to more difficult trials in which the animal had to watch longer and neurons where ramping slower and not as high. Threshold for eye saccade and decision was a firing rate of 70 spikes per second on average(Gold and Shadlen, 2007).

II.2.3. Multisensory decision making
Different sensory systems can receive different sensory information in parallel, but their estimation of the real world may contradict. However the animal might use a combination of sensory inputs to make a decision (Bizley et al., 2016). How does this multisensory integration happen? The classic theory of multisensory decision-making says that stimuli have to be synchronous. Thus, it is interesting that auditory and visual stimuli drive neurons with different latencies (Recanzone et al., 2000). A group tried to investigate if auditory and visual information in combination lead to a better performance in a stimulus discrimination decision-making task (Raposo et al., 2012). Auditory and visual stimuli trains where generated separately and therefore enabled stimuli-presentation varying from synchronous to non-synchronous. Rats and humans had to listen and accumulate evidence over time to be able to perform frequency discrimination. Results showed that in both, humans and rats, the decision accuracy was significantly enhanced in multisensory trials compared to singular auditory or visual trials only (Raposo et al., 2012). The study claims 3 findings: Subjects can combine multisensory information for decisions in a sequential manner. They showed multisensory enhancement when sensory inputs where presented independently. Multisensory enhancement can be found in humans and rats and hence might be general and not restricted to distinct species (Raposo et al., 2012).
There are two different theories suggested (Bizley et al., 2016) about how sensory information of two different sensory systems could be integrated: It is called “late integration” when e.g. auditory cortex and visual cortex work in parallel without early exchange of information. Evidence accumulation happens separately in auditory and visual cortex. Both areas make a decision and the

combination of both leads to a final decision and motor response. In “early integration” an immediate exchange of information between the sensory cortices takes place. Permanent multisensory exchange leads to final decision.
To address causality of multisensory decision-making, not only behavioural experiments but also neural manipulating methods are needed. Questions could be answered, such as: if neurons are involved in the cross-modal integrating process, are they really contributing to a decision? To determine if late or early multisensory integration happens, approaches addressing functional connectivity like optogenetic inactivation or activation with the ability of temporal control are suggested (Bizley et al., 2016).

II.3. Evidence accumulation

Recently the decision process of sequential analysis has been further described as *evidence accumulation* (Brunton et al., 2013). In this model, also called evidence integration model, a subject is collecting and accumulating evidence for one or the other choice in its mind gradually. The result of the accumulation will drive the animal’s decision (Brody and Hanks, 2016). The model says that if the accumulated value of evidence for one choice is reaching a certain threshold, called “decision boundary”, then this decision is executed. If evidence is weak, the value of evidence grows slowly and reaches the decision boundary late or never, enlarging more along the “decision boundary” (Brody and Hanks, 2016).
In contrast to the drift-diffusion model, which assumes that the brain accumulates evidence over time driven by a stimulus (drift), which is disturbed by noise (diffusion) (Bitzer et al., 2014; Ratcliff and McKoon, 2008), it could be shown that evidence accumulation maintains and adds evidence to its memory. In a two-alternative-choice task rats and humans had to listen to click-trains with a stable total frequency of 50Hz to assess which side of the head most clicks were presented on. For humans the same task was additionally transformed into a visual task, where subjects had to observe flashing white bars with either rightwards or leftwards orientation. Using a mathematical best-fit model, it could be shown that in 13 out of 19 rats and in all human subjects in both, auditory and visual task, the value best fitting for drift-diffusion noise was zero. Therefore it seems that the brain is capable of accumulating evidence without noise disturbance (Brunton et al., 2013), which stands in big contrast to conditional probability Bayesian coding hypothesis (Knill and Pouget, 2004).

II.4. Posterior parietal cortex and its function in perceptual decision making

Lesion studies on humans and primates showed that unilateral damage causes contralateral irresponsiveness to stimuli, characterised as a lack of attention instead of problems in perceptual stimuli processing (Bucci, 2009).
In studies on monkeys, Shadlen and Newsome (1996) performed visual perceptual decision-making experiments in which the individuals had to solve a “random dot motion discrimination” task. They found that neurons located in the posterior parietal cortex showed firing rates ramping over time. This neuronal activity ramped faster in easy trials according to what is expected for the evidence accumulation. Thus there may be a correlation between evidence accumulator and posterior parietal cortex activity. A similar firing pattern was recorded in frontal eye fields, superior colliculus and striatum (Brody and Hanks, 2016).
Recently, Brunton et al. (2013) developed a perceptual decision making task for rats depending on gradual evidence accumulation, called the “Poisson click” task. Rats had to listen to Poisson randomly distributed audio clicks presented simultaneously on both sides of the rat’s head and decide on which side the most clicks were presented within a trial. Using this task, neurons were recorded in the posterior parietal cortex and frontal orienting fields of rats (Hanks et al., 2015). Neurons, which exhibited growing firing rates during decision making, with steeper ramping for easy

trials, were recorded, as expected, in trials with stronger evidence and in both regions. Notably, neurons in frontal orienting fields were climbing more stepwise in firing rate compared to posterior parietal cortex neurons. Therefore it is suggested to read frontal orienting fields activity more as a categorical decision indicator while posterior parietal cortex seems to function as the accumulating force (Hanks et al., 2015). Optogenetic inactivation studies confirmed the hypothesis that frontal orienting fields play a main role in categorising possible choices (Brody and Hanks, 2016).
Remarkably, inactivation experiments addressing the role of several cortical regions found that the posterior parietal cortex, thought to be mandatory for evidence accumulation, is rather reflecting the accumulation process than necessarily needed for decision-making (Erlich et al., 2015). In more detail, unilateral silencing of posterior parietal cortex did not have an effect on correct decision making in the evidence accumulation task (Erlich et al., 2015). It did have an effect on free choice trials though, in which the animal could chose freely to receive reward, by causing an ipsilateral side bias (Erlich et al., 2015). Also, when posterior parietal cortex was inactivated, no impairment on decision making was found in mice or primates. Thus it seems that neuronal silencing of posterior parietal cortex has little to no effect on decision making based on evidence accumulation. Beside medial prefrontal cortex, superior colliculus, striatum and frontal orienting fields, posterior parietal cortex is the only area where silencing had no impact on task solving behaviour (Hanks et al., 2015).

III.
Representation of Decision Confidence in the Orbitofrontal Cortex

III.1. Approaching the role of orbitofrontal cortex in adaptive behaviour

III.1.1. Response-inhibition and flexibility

The orbitofrontal cortex as a sub-region of the prefrontal cortex has been tested for several functions in goal directed decision making like the encoding of reward value (Schoenbaum et al., 2011), appetite and aversive stimuli (Tremblay and Schultz, 1999). As well lesion studies have been done showing the orbitofrontal cortex's involvement in devaluation- or rule reversal tasks (Schoenbaum et al., 2009).

So far, the orbitofrontal cortex was believed to play an important role in behavioural flexibility as observed in reverse conditioning. Lesion studies on rats (Fellows and Farah, 2003; Hornak et al., 2004; Schoenbaum et al., 2003) showed an impaired response to rule reversal, suggesting that the orbitofrontal cortex could be inhibiting unwanted behaviour. However, studies determined that subjects were able to learn response inhibition in a reversal task despite the presence of orbitofrontal lesions or damage (Schoenbaum et al., 2009). Also in monkeys, orbitofrontal inactivation had no impact on value-based decision making, where the subject had to choose the smaller reward of two in order to receive an even bigger reward. Thus it seems that the orbitofrontal cortex does not play a great role in response inhibition (Schoenbaum et al., 2009). Also anatomical studies show that the orbitofrontal cortex contains fibres passing from the temporal lobe to the prefrontal cortex, indicating that response inhibition is rather mediated by prefrontal areas (Stalnaker et al., 2015).

Nonetheless, the orbitofrontal cortex did show encoding of new associative information. In reversal studies on monkeys single neuron recordings exhibited units in the orbitofrontal cortex reversing their firing response due to reversed conditioning (Thorpe et al., 1983). Importantly, it has to be mentioned that only 25% of orbitofrontal neurons reversed their cue specific firing pattern. Other brain regions changed their firing more rapidly and in greater proportion, like for example neurons in the rat basolateral amygdala with an amount of 44-60% (Schoenbaum et al., 1999).

To conclude, the orbitofrontal cortex seems not to have a special role in response inhibition nor it is more active in encoding of new associative information (Schoenbaum et al., 2009). Error updating experiments showed that dopaminergic neurons in the ventral tegmental area and nucleus accumbens were predicting error updating, but neurons of the orbitofrontal cortex did not (Stalnaker et al., 2015).

III.1.2. Reward anticipation and value

Orbitofrontal neurons fire specifically in anticipation of a reward (Fig 2, (Schoenbaum et al., 2009)). Rats respond faster when sampling a cue related to a positive outcome compared to trials in which a cue signalled a negative outcome (Schoenbaum et al., 1998; Schoenbaum et al., 2003).

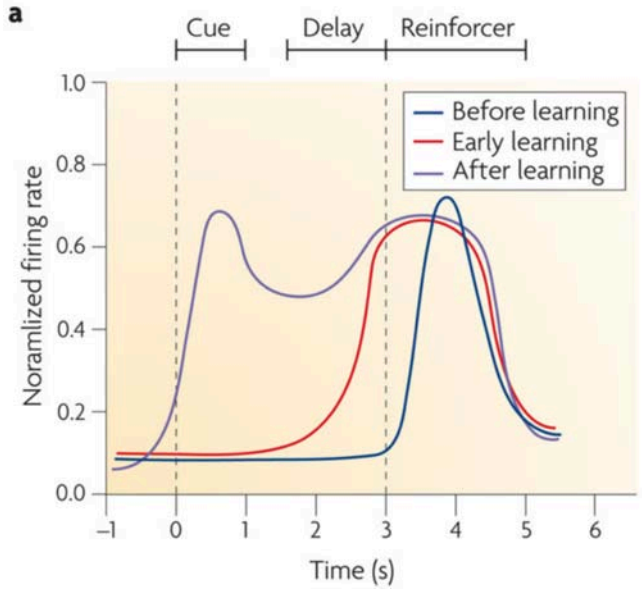

Fig. 2, Reward response of neurons in the orbitofrontal cortex (Schoenbaum et al., 2009). Initially, neurons in the orbitofrontal cortex typically fire only when the reward is delivered(blue line). After some trials animals show neuronal response also in anticipation of the following reward (red line). Later they show a second peak as a consequence to reward related cue presentation when task is already learned (purple line).

Value can be described by a single scalar variable and can be represented by firing range of a single neuron. It is always consisting of negative and positive components, value = benefit – costs (Mainen and Kepecs, 2009). According to decision studies it seems that the orbitofrontal cortex encodes subjective value about decisions and their possible rewards (Mainen and Kepecs, 2009). Responses could be altered by associative learning and hunger or satiety experiments. Not only reward as a positive stimulus per se makes orbitofrontal neurons fire but also the omission of negative effects like punishment lead to orbitofrontal response (Hosokawa et al., 2007). Important in the concept of value is the ability of changing a reward given its value depending on available alternative rewards and economic circumstances, which has been shown for orbitofrontal neurons in monkeys (Tremblay and Schultz, 1999). In contrast, a recent study showed the opposite result, stating that cells fired independently of alternative reward options (Padoa-Schioppa and Assad, 2008). In devaluation studies, in which a Pavlovian cue gets devaluated by reward reduction or pairing with illness, lesions in the orbitofrontal cortex impaired the devaluation effect. Lesions had also disabling impact on Pavlovian-to-instrumental transfer tasks (Ostlund and Balleine, 2007).

Furthermore neurons in the orbitofrontal cortex appear not to integrate information about reward value. They show no differentiation between small or big reward sizes (Roesch et al., 2006). In comparison, neurons in the ventral striatum and midbrain strongly signal reward size (Schoenbaum et al., 2011). Talking about economic value, the preference among familiar rewards was unaffected in cases of the orbitofrontal cortex damage. This might be due to a certain preference history, a memory about former reward values (Stalnaker et al., 2015).

These findings underline the purpose of orbitofrontal cortex to drive behaviour due to anticipation (Schoenbaum et al., 2009). Orbitofrontal neurons fire actively in anticipation of an event but are not triggered as a consequence of it (Schoenbaum et al., 2011). Furthermore, the internal state of the subject can modulate neuronal representation of value, e.g. the state of hunger enhanced the firing response of orbitofrontal neurons in response to reward (Critchley and Rolls, 1996).

III.1.3. Representation of spatial goals

Since the orbitofrontal cortex is in a reciprocal connection with the posterior parietal cortex, medial granular cortex and medial prefrontal cortex, which are important for spatial navigation in goal-directed behaviour (Lipton et al., 1999), the question of importance of the orbitofrontal cortex in special navigation arose. Thus, a two-alternative choice task was performed to address the importance of the orbitofrontal cortex in spatial goal representation (Feierstein et al., 2006)**.** Using information of odour cues, rats had to decide whether to go to the left or right hand side. Neuronal recordings were performed in the ventrolateral and lateral orbitofrontal cortex as well as in the agranular insular cortex. 5.8% of recorded cells were found to carry information about the animal's choice before response initiation (Feierstein et al., 2006)**.** Examining the selectivity for the direction of choice, 41% of recorded cells in the left orbitofrontal cortex were selective for response direction, symmetric for left and right choices. 35% of the location selective cells were active while rats were at the goal port. In total, 56% of the recorded cells were either left or right tuned and responded in both response or outcome period (Feierstein et al., 2006)**.** Confirming the direction sensitivity one cell was recorded firing when the animal was leaving the centre port to the left side and also when the animal was leaving the right port but making a turn to the left. Interestingly, in the population of neurons responsive for outcome anticipation period some are only active in error trials; others showed selectivity for correct trials only. These neurons are interpreted as encoding outcome and goal location in combination. Concluding these observations the orbitofrontal cortex was interpreted as strongly encoding spatial and motor information, being involved in the process of goal and direction finding (Feierstein et al., 2006).

III.2. The orbitofrontal cortex, reflecting decision confidence

III.2.1. Decision confidence in rodents

Human confidence is believed to result from a metacognitive process of evaluating and reflecting previous and current decisions. In fact, neurons in the orbitofrontal cortex of rats were found with activity being interpreted as strongly representing decision confidence (Kepecs et al., 2008). In this two-alternative forced choice odour mixture categorisation task in each trial a binary odour cue was delivered consisting of 2 pure flavours mixed in a certain ratio. Ratio of the odour mix was created new for each trial in a random manner. The boundary for category left or right was at an odour ratio of 50:50. By varying the distance of the stimulus from the boundary, the difficulty could be changed. In trials in which odour A was represented in higher amount, left was the correct choice, higher amount of odour B was the indication for right choice. Single neurons in the orbitofrontal cortex were recorded, showing modulation in firing depending on stimulus difficulty during the reward anticipation period (Kepecs et al., 2008). There were neurons firing with a higher rate for difficult trials in which stimuli were very close to the categorical boundary. Other neurons tended to fire with higher frequency in easy trials, in which one of the odours was present at a far greater concentration than the other (Fig. 2. e, f, (Kepecs et al., 2008)).

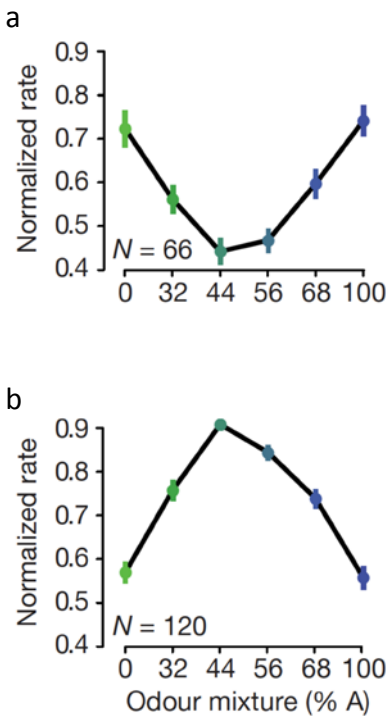

Fig. 3 a, b, Population response in the orbitofrontal cortex showing higher firing rate during trials of high odour discriminability (a); example neuron showing high activity specific for trials of low discriminability (b) (Kepecs et al., 2008).

More recently, for further investigations on decision confidence, a *post decision wagering task* was designed. This task is based on the subject's willingness to wait for reward after making a decision in an odour-two-compound-discrimination task (Lak et al., 2014). Rats received an olfactory stimulus, composite of two distinct odours in a certain mixture ratio. Ratio was changing from trial to trial in a random manner (20:80, 40:60, 44:56, 50:50). Animals had to indicate which compound was most present by poking into one of two possible nose ports where water, in consequence of a correct answer, was delivered. Reward was delayed, varying from trial to trial by an exponential distribution with a decay constant $T_{1/2}$ = 1.5. If the rat wasn't waiting long enough and left the port, it received no reward but could initiate a new trial. Also in incorrect trials animals were not signalled that they were wrong, and left the reward port after a freely-chosen waiting time and without reward. To estimate the subject´s level of confidence, *catch trials* were introduced with a probability of 10-15% occurrence. In these trials no reward was delivered, independent on the animal's choice. Thus, in catch trials waiting times for reward were measured, interpreted as confidence report (Lak et al., 2014).

The Kepecs group developed a *normative temporal wagering model,* which could predict exactly the animals' behaviour and confidence.

Reward expectation function: $P(R|W_t)=\frac{P(Wt|R)P(R)}{P(Wt)}$

t…Time spent in the port without receiving a reward

W_t...Event that waiting time until time t was not rewarded

R…Event that reward arrives at the next moment, from t to t + dt

$P(W_t|R)$= 1...Probability of waiting without reward given that reward arrives in the next moment is 1

Probability of getting the reward at the next moment: $P(R)=P_{trial} \times P_{rew}(t)dt$

P_{trial}…Expectation of being rewarded in the current trial for the given choice

P_{rew}…Experimenter-defined temporal distribution of reward during the anticipation period

They found results consistent with the mathematical model (Lak et al., 2014). Decisions in trials with longer waiting time had a higher accuracy. When trials were separated in long and short waiting time trials, choice accuracy with intermediate odour mixture difficulty (20% contrast) was significantly different depending on waiting time, meaning longer waiting time for correct catch trials in

intermediate trials and shorter waiting time for incorrect trials. They showed that rats' waiting times varied with trial difficulty. Regarding to these findings waiting time for reward can be used as report for decision confidence (Lak et al., 2014).
Transient inactivation of the orbitofrontal cortex by the GABA-A agonist Muscimol did not alter the rats' performance or reaction time compared to control saline injections. However, it did change the subjects' waiting times which was no longer not significantly different between correct and incorrect trials. Therefore, the orbitofrontal cortex seams not to be necessary for perceptual decision making but reflects the animal's confidence about committed decisions (Lak et al., 2014).
In another study, using a mixture of GABA-A agonist Muscimol and GABA-B agonist Baclofen, the orbitofrontal cortex was inactivated during a rodent betting task (Barrus et al., 2016). After injection, animals were more sensitive to wagering. In 40% of trials orbitofrontal inactivation resulted in choosing the risky reward option, with a chance to get double the amount or nothing. Controls were deciding for wager in only 20% of trials, showing a higher preference for the safe reward option (Barrus et al., 2016).

III.2.2. Decision confidence in humans

To compare decision confidence observed in rats to decision confidence observed in humans (Sanders et al., 2016), an auditory perceptual decision making task (Brunton et al., 2013) was introduced. First, using a Monte Carlo simulation, confidence and accuracy of a two-alternative forced choice perceptual decision task could be predicted. In this model a choice was correct if external evidence and internal percept matched. Statistical confidence was found to predict the mean choice accuracy (Fig. 4a, (Sanders et al., 2016)), also statistical confidence for a given discriminability increased for correct and decreased for incorrect choices (Fig. 4b, (Sanders et al., 2016)). Notably average confidence for trials of zero evidence discriminability was predicted to be higher than expected chance accuracy (0.5) with a confidence level precisely at mid-level 0.75 (Fig. 4b, (Sanders et al., 2016)). Decision accuracies spanned from 0.5, chance, and approximately 1, perfect. The simulation predicted the accuracy to be higher for high-confidence choices compared to low-confidence choices with lower accuracy (Sanders et al., 2016).

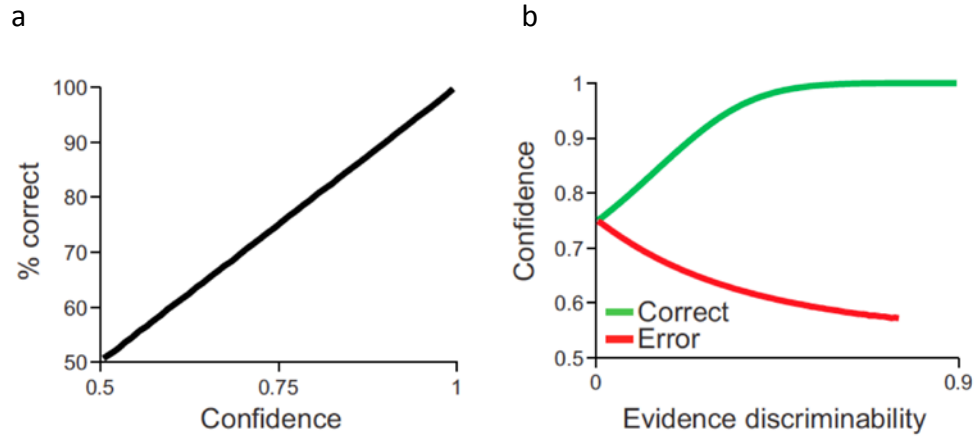

Fig. 4 a, b, Confidence predicted mean choice accuracy (B), Confidence increased in correct trials and confidence decreased in incorrect trials with increasing evidence discriminability. Zero evidence discriminability predicted a confidence level of 0.75 (C) (Sanders et al., 2016).

The model was then tested in an auditory perceptual decision making task on 22 human subjects. Volunteers were listening to two separate but parallel Poisson distributed click trains with the goal to report which of the two trains was containing a higher amount of clicks. Trials with neutral evidence had a click frequency of 50Hz for both click trains, strong evidence was given in trials with 65Hz/35Hz click presentation. This resulted in task accuracy from chance to almost perfect. Subjects had to report their level of confidence after each decision by choosing a value, 1 stood for random guess and 5 for high confidence. Before starting the experiment subjects were trained and difficulty was

individually adjusted to have a mean performance of approximately 80% in all participants (Sanders et al., 2016).

Matching to the predictions of the Monte Carlo Model, the human trials showed that confidence strongly predicted choice accuracy (Fig. 5a, 5d, (Sanders et al., 2016)), self-reported confidence increased for correct trials and decreased for incorrect decisions (Fig. 5b, 5e, (Sanders et al., 2016)), trials with zero evidence discriminability got a confidence rating of 3 in the 5-division scale (Fig. 5b, 5e, (Sanders et al., 2016)) which agrees with the model with a mid-range confidence (0.75) and importantly, high or low confidence reports predicted high or low choice accuracy (Fig 5c, 5f, (Sanders et al., 2016)).

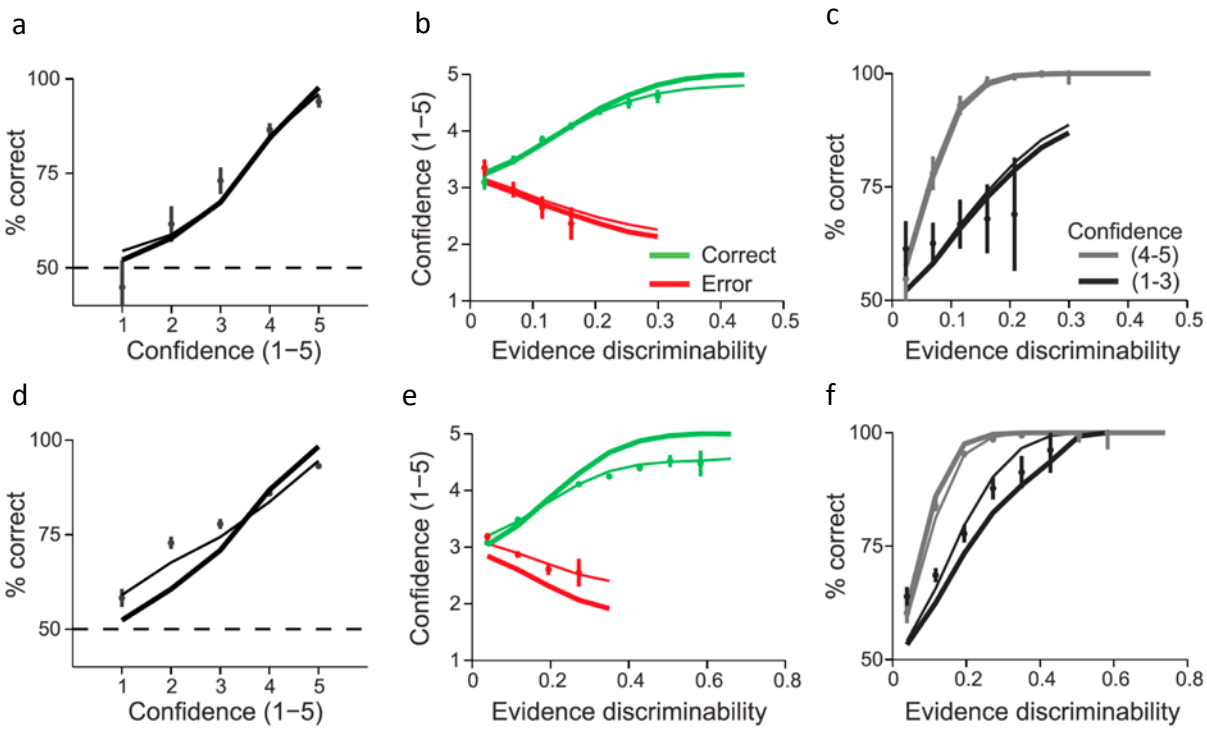

Figure 5, a-f, Confidence report of the human trials (Sanders et al., 2016). Evidence discriminability is defined as the ratio of the absolute click number difference between left and right side and the total number of all clicks $|((L-R)/(L+R))|$. Confidence report of a single participant. Thick lines show parameter-free task simulations (Monte Carlo), thin lines show subject's task outcome. Data of all 5 subjects show the same pattern.

To assess if this model is also suitable for human every-day-life decisions, the experiment was repeated similarly but participants had to tell which of two countries had a larger population. In this version subjects did not get feedback to their answers to avoid the learning effect. Results were again confirming the model's prediction (Fig. 6, (Sanders et al., 2016)).

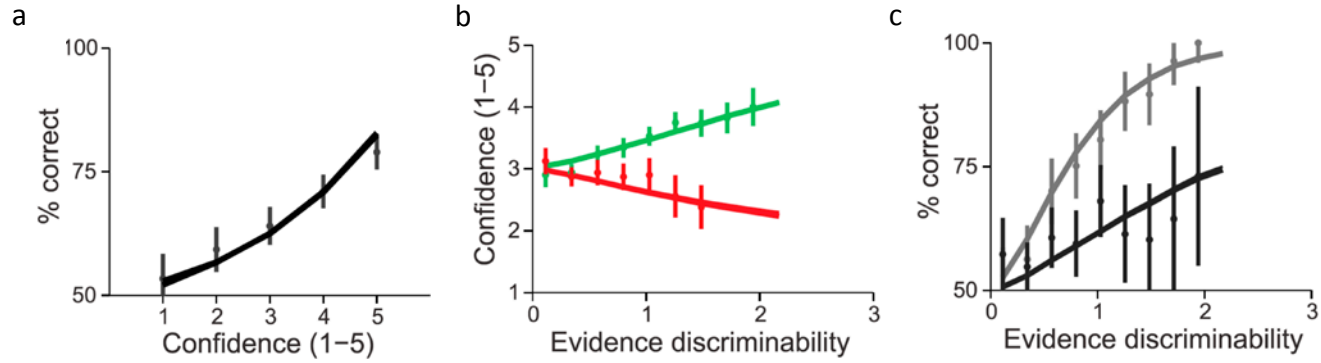

Fig. 6, a-c, Combined data of 27 participants in a general knowledge decision making task gave same results about decision confidence (Sanders et al., 2016).

III.3. Bayesian probability and mathematical background of decision confidence

Signal detection theory in a discrimination task draws two overlapping distributions, each representing the likelihood of a stimulus. If one of the two distributions is the correct one, then the other distribution is noise. For making a decision the noisy observation is converted into a *decision variable*. The limitation of signal detection theory is that it does not include any information about time. Time is directly linked to confidence. Since evidence accumulates over time, the subject's confidence might vary with time (Fetsch et al., 2014).
Sequential analysis can be seen as an extension of signal detection theory including time, based on *bounded evidence accumulation*, *drift-diffusion* and *race models*. It is representing both time and evidence, since the time point on which enough evidence has been accumulated to make a decision is associated with a certain probability that the decision was correct (Fetsch et al., 2014).

III.3.1. Decision confidence in Bayesian probability

At the level of populations of cells today's neuroscience tends to use the theory of probabilistic coding when considering the brain's information processing. Since decision confidence is getting more and more popular in this field it is suggested to use the Bayesian probability as definition for subjective confidence (Meyniel et al., 2015).
There are two terms in use, which are actually exactly opponent to each other: *confidence* in the metacognitive field, which can be described by a single number like a rating and *uncertainty* in Bayesian computational field, what can hold a whole distribution of numbers. Therefore, there are also two types of confidence, the *summary confidence* and the *distributional confidence*. The *summary confidence* is derived from the *distributional confidence* calculated by the brain. A theory known as *probabilistic population coding* assumes that in a population of neurons each of them is reacting to a given stimulus orientation. Neurons will be less or more stimulated by the presented cue. As a result, the sum of firing rates will then give information about the likelihood that a stimulus has a certain orientation. The *Bayesian sampling theory* is very similar but takes the activity of only one single neuron at a particular moment as an interpretation of the stimulus orientation. Thus whole populations of neurons represent entire probability distributions, which can be conveyed into confidence. This representation of confidence is what is called *distributional confidence* (Meyniel et al., 2015). The precision of a neuronal stimulus representation is simply based on the number of activated cells. Confidence readout would then be as simple as linear summation (Fig. 7, (Meyniel et al., 2015)).

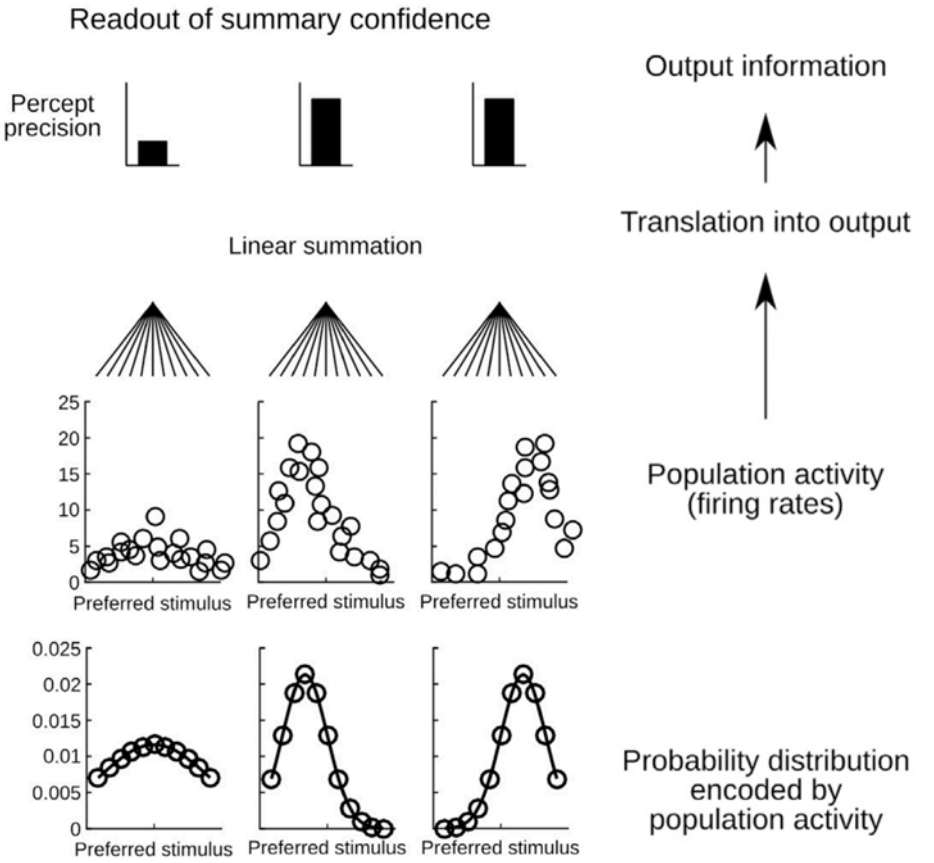

Fig. 7, Bayesian sampling theory. Populations of neurons represent entire probability distributions, which are conveyed into confidence (= distributional confidence) (Meyniel et al., 2015).

For confidence augmentation in a decision process it is suggested that confidence could follow the rule of evidence accumulation, during which a decision value has to rise over time until it reaches a boundary assigned for one or the other decision. Linear integration of neuronal activity could lead to a certain confidence level, which has to reach a certain threshold for taking a goal directed action (Meyniel et al., 2015).

An experimental approach to measure decision confidence is creating a two-alternative choice wagering task in which animals can indicate their confidence level by their willingness to pay a wager (e.g. waiting time) for each decision, in order to receive reward (Lak et al., 2014). Showing a high level of confidence is based on high evidence levels (Kepecs et al., 2008). This means different brain areas, important for decision making, are feeding the orbitofrontal cortex with gathered information. Yet, since the orbitofrontal cortex is not directly involved in decision making itself, silencing of this area is disturbing animal's decision confidence reports but not their ability to make correct decisions (Lak et al., 2014).

III.3.2. Statistical decision confidence prediction (Monte Carlo simulation)

Formally, decision confidence can be defined as a probability estimate that the chosen hypothesis is correct, given the available perceptual evidence. Perceptual evidence can be referred to as the percept. The percept is a variable internal to the decision maker (Hangya et al., 2016). Furthermore, the percept of a stimulus leads to a choice. Percept and choice together influence the internal evaluation of confidence. Confidence then represents the internal feeling of accuracy (Fig. 1A, (Sanders et al., 2016)).

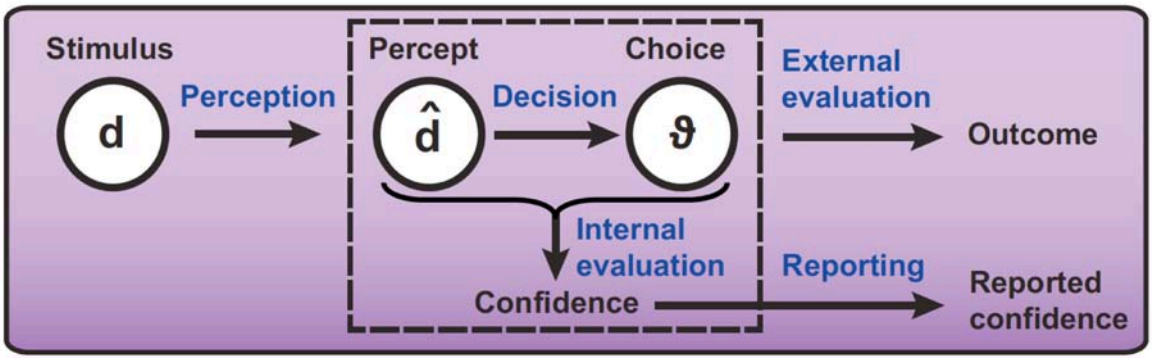

Fig. 8, Illustration of the statistical concept for decision confidence formation (Sanders et al., 2016). Percept $\hat{d}$ and choice ϑ are internal for the decision maker. A stimulus d is processed due to perception. $\hat{d}$ is the resulting internal representation of d and is used to make a choice ϑ. The evaluation of percept and choice will lead to a certain confidence level.

Confidence as an objective mathematical quantity can be defined as the Bayesian posterior probability, giving a formal definition of statistical confidence (Hangya et al., 2016).
A decision is a commitment to one of several possible options. Statistically spoken, a hypothesis (H_1, alternative Hypothesis) is chosen, which stands against the other alternative choices (H_0, Null hypothesis). H_1 assumes that the choice is correct and H_0 says that the decision was incorrect (Sanders et al., 2016). The Bayesian posterior probability quantifies the degree of belief in the correctness of a chosen hypothesis (Hangya et al., 2016). The Bayesian posterior probability concept therefore describes confidence as $c=P(H_1 \mid \hat{d}, \vartheta)$. The Gaussian noise model is $P(\hat{d} \mid d)$, while for each trial d is drawn from a pool of ds with equal probability. Choice is a stochastic function of d: $\vartheta = \theta(\hat{d})$ (Sanders et al., 2016).

d… stimulus, $\hat{d}$…percept of d, ϑ…decision/choice

There are four major conclusions about decision confidence drawn from the simulations: 1st Confidence predicts accuracy, 2nd confidence increases with evidence discriminability for correct choice and confidence decreases for incorrect choices with increasing evidence discriminability, 3rd when evidence discriminability is zero (50:50) the mean decision confidence is 0.75 (Sanders et al., 2016), 4th evidence discriminability predicts accuracy but confidence (reward anticipation time) provides even more information making the prediction more accurate (Hangya et al., 2016).
Computational models predicting behaviour variables can serve as proxies for unobservable variables guiding decision making. Such computational models are only interpretational tools and will never be able to represent the whole truth (Kepecs and Mensh, 2015).
An open question is, if the orbitofrontal cortex computes confidence locally or if it receives the signals from other brain areas (Kepecs and Mensh, 2015). Studies showed neuronal activity of the parietal cortex as well as in the pulvinar nucleus of the thalamus correlating with decision confidence (Kiani and Shadlen, 2009; Komura et al., 2013).

IV.
Memory-Guided Decision Making

IV.1. Working memory and the prefrontal cortex

Working memory is a very important feature of the mammalian brain, especially needed for decision making, since it provides temporal organisation, internal processing and preparation of information to plan and execute future goal-directed behaviour in further consequence (Baddeley, 2003).
Observations in the dorsolateral prefrontal cortex of monkeys exhibited neurons firing persistently during delay phase in an oculomotor delayed-response task. In this experiment monkeys had to fixate a central spot on a screen while a peripheral cue was presented. After cue presentation and a short delay period (1-6 sec) subjects had to indicate the cues former position by making an eye saccade to the according side. Due to their activity in the delay period, these cells were described as delay cells (Funahashi et al., 1989). It was found that delay cells in the prefrontal cortex fired sustainably in the delay period but ended with execution of behaviour (Srimal and Curtis, 2008). Furthermore it was shown that those delay period specific cells are most likely spatially tuned. This tuning means that single cells specifically fire in response to cue location during delay and fire much less or are even inhibited while waiting to respond to a cue that has been presented on the contrary side. This firing pattern was called memory fields (Goldman-Rakic, 1995). Interestingly, not only pyramidal cells but also fast spiking interneurons in the dorsolateral prefrontal cortex display the nature of memory fields, playing a role in spatially oriented inhibition (Rao et al., 1999). Further inactivation studies using iontophoretic bicuculline methiodide application, blocking $GABA_A$-receptors in the dorsolateral prefrontal cortex of monkeys, led to inhibition of pyramidal cells and putative interneurons during a delay period in an oculomotor delayed response task (Rao et al., 2000). These observations strengthened the hypothesis, that the prefrontal cortex of primates is needed as a working memory compartment, which keeps goal directed information ready for use when goal directed behaviour needs to be expressed (Goldman-Rakic, 1995).
However, more recent findings suggest that the maintained activity of prefrontal neurons during a delay period might not serve to keep information in working memory. Instead, it may have a top-down influence on primary sensory regions of the cortex to bias stimulus specific activity (Sreenivasan et al., 2014).
Working memory related coding of information has been observed in the rodent prefrontal cortex as well. In a spatial exploration task rats were placed on a radial eight-armed maze. Recorded cells in the medial prefrontal cortex showed different firing patterns when comparing activity before and after the first visit to one of the arms. The change in firing for already visited arms has been described as tagging and is suggested to be a function of working memory and information storage (de Saint Blanquat et al., 2010). The claim that the prefrontal cortex plays a major role for working memory was supported by the observation of single medial prefrontal neurons firing specifically for goal direction during performance in an odour-based delayed match-to-sample task (Fujisawa et al., 2008). However, also in purely spatial working memory tasks, medial prefrontal neurons of rats exhibited activity during delay periods as well as changes in firing, seeming to encode previous and future goal choices (Baeg et al., 2003). Taken together, working memory in the rodent prefrontal cortex may be based on sequential activation and inactivation of neuronal assemblies.
In addition to the medial prefrontal cortex, the hippocampus, ventral tegmental area and medial prefrontal cortex have been reported to be areas important for working memory. All three are synchronised by a 4-Hz-oscillation during working memory. Goal-predicting pyramidal cells of the prefrontal cortex were even more phase-locked to hippocampal theta oscillation and 4-Hz-oscillation than non-predicting cells (Fujisawa and Buzsaki, 2011). Furthermore, firing correlated to theta oscillations of medial prefrontal and hippocampal neurons was enhanced during behaviour involving spatial working memory in rats. These findings indicate that spatial information found in the

hippocampus is passed on to prefrontal areas for further processing and integration into working memory (Jones and Wilson, 2005).

IV.2. Effects of prefrontal cortex inactivation on working memory

In a working-memory-dependent conditional discrimination task, rats learned to choose the correct of two goal arms of a maze considering the floor texture of the maze corridor. The experimenter changed floor insert before each trial. The floor insert only covered half of the corridor, meaning the animal had to keep the cue information in mind while being on the way to the goal arm juncture. Inactivation of the medial prefrontal cortex by the $GABA_A$-agonist muscimol led to strong performance impairment (Fig. 9, (Urban et al., 2014)).

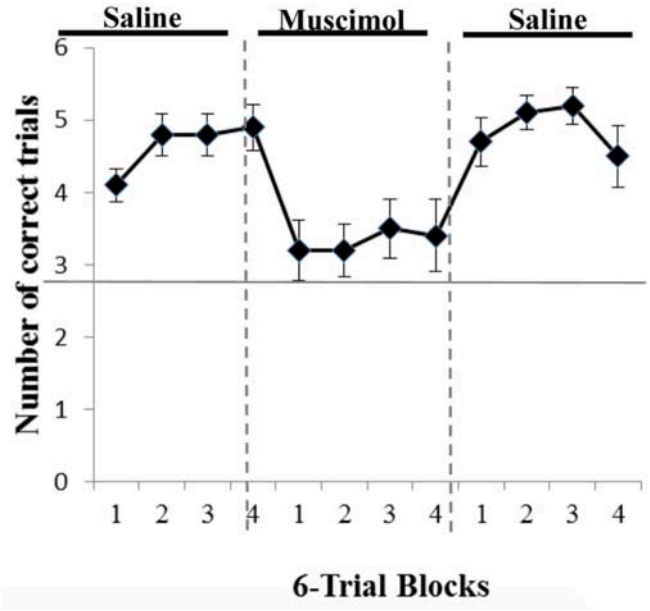

Fig. 9, Inactivation of medial prefrontal cortex results in performance impairment (Urban et al., 2014).

Another inactivation study on rats showed similar results for muscimol injection into dorsomedial prefrontal cortex underlining the importance of the prefrontal cortex in goal directed behaviour based on working memory capacities (Fig. 10, (Horst and Laubach, 2009)).

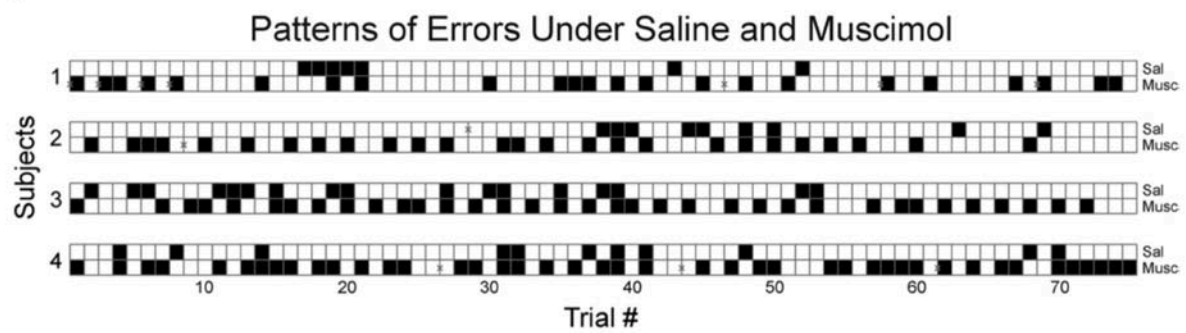

Fig. 10, Patterns of decision errors for muscimol inactivation or saline control experiments (Horst and Laubach, 2009).

V.
Methods

V.1. Auditory Two-Alternative-Post-Decision-Wagering Task

V.1.1. Experimental Subjects

All procedures on animals were performed under an approved licence of the Austrian Ministry of Science and Medical University of Vienna.
For this study 4 Long-Evans rats (350-500g) were group housed and kept in a 12-hour light-dark cycle. Water was removed every Sunday between 10am and 2pm to induce water restriction. Animals received a minimum water amount between 4-7 ml within the next 24 hours on training days. During training, the achieved water-maxima were approximately 15 ml a day. On Fridays, in the afternoon, water restriction was intermitted for 36 hours until next removal on Sundays. For handling and keeping the animal motivated during the task, rats were fed with KELLOGG'S® FROOT LOOPS®.
Between training and for handling and health reasons animals were put into an enriched environment, equipped with a running wheel, rodent houses and paper for nest construction.

V.1.2. Behavioural Training

Rats were water restricted for two days before the start of training. Weights were taken each day to keep track of animal's health. Also cage movement and social interaction was observed as well as possible porphyrin secretion in eyes and nose as sign for stress. Body weights during restriction phase never dropped below 85% of initial body weight, which was taken on Sundays when water was removed.
Rats were trained in an auditory two-alternative-post-decision-wagering task based on evidence-accumulation (Brunton et al., 2013; Lak et al., 2014; Sanders et al., 2016). For each training session animals were placed into a soundproof behavioural box. This box contained three nose ports and two unreachable speakers presenting the auditory cue on left and right side of the animal's head. A trial was initiated by the subject poking into the centre port for durations of more than 200-350 ms. Trials with a centre poke shorter than 200-350 ms were aborted. While poking into the centre port, animals had to listen to two - in parallel - presented click trains deriving from each of the two speakers with a total click rate of 50 Hz. A training session had in general a set distribution of stimulus difficulties but difficulty for each trial was always randomised. Trial difficulty is defined as the ratio between the amount of right and left clicks. The click trains were generated by a Poisson distributing process, resulting in a slow click and a fast click train, depending on the number of generated clicks per second. To avoid the chance that subjects were guessing the correct side considering only the very first click, which often indicates which is the fast click train, first click was played in stereo from both sides. Animal should listen to the clicks and accumulate evidence for the side with the higher amount of clicks in each trial. After the minimum sampling time of 200-350 ms the rat could leave the centre port whenever it was ready to give an answer. By deactivating the centre port, sensors of side ports were free to enter. For each correctly given answer animals received ~ 20 µl after a random delay between 0.5 and 8 sec, in which the ports must not be left. For incorrect poking or leaving the port too early the animals received no water as punishment. When rats reached a performance of 80% accuracy, a small percentage (10-15%) of catch trials were introduced in which the time spent was measured while the rat was in either of the two side ports. The idea of catch trials is that the animal never received water, even for correct trials. Due to the task conditions, animals waited a random time until water delivery. By measuring the time the rat is willing to wait in one of the side ports in anticipation of reward, it is assumed to measure the animal's level of decision confidence. More time investment indicates high decision certainty or confidence, less time investment indicates uncertainty.

V.2. Delayed cue-matching-to-place-task

V.2.1. Experimental Subjects

All procedures on animals were performed under an approved licence of the Austrian Ministry of Science and Medical University of Vienna.

4 Long-Evans rats (350-500 g) were group housed and kept in a 12-hour light-dark cycle. Animals were food-deprived to 85% of their initial bodyweight for best performance. On restricted days rats were fed with two to six 5 g-rodent-food pellets.

Between training and for handling and health reasons animals were put into an enriched environment, equipped with a running wheel, rodent houses and paper for nest construction. Physical abilities and navigation on the maze seemed to be improved by the environmental enrichment. After implantation animals were separated from littermates and kept solitarily.

V.2.2. Behavioural Training

Rats were food restricted one week before training onset to 85% of their initial body weight. They were trained on a Y-maze to perform a delayed cue-matching-to-place-task (Fujisawa et al., 2008). In this paradigm animals learned to match stimulus information (18 µl chocolate- or cherry- solution, both containing 15% sugar), presented on the home arm, with reward (68 µl of presented stimulus solution), delivered in one of the two choice arms, in case that chosen direction was correct. If the stimulus was cherry the rat had to go to the right arm, if stimulus was chocolate it had to choose the left arm in order to receive reward. The sequence of stimulus presentation was randomised. In order to avoid odour-guided strategies, odour-distracters (tissue dipped into both solutions) were placed at the end of both choice arms and maze was cleaned after each session. Once the animal reached an accuracy of minimum 85% over more than 100 trials, a movable gate was introduced on the stimulus arm, which was closing behind the animal when it entered for stimulus evaluation and opened again to let the subject execute its decision. The delay caused by the gate was gradually prolonged from session to session until animals reached 85% accuracy again with a final delay of 6 sec following the end of stimulus presentation.

V.2.3. Surgery and Pharmacological Inactivation of Prelimbic Cortex

Duratomies, craniotomies and injections were performed under isoflurane (Forane®, AbbVie, induction: 4%, maintenance: 1-2%, oxygen flow: 2 l/min) anaesthesia and analgesic (0.2 ml Xylocain® 2% and metacam® 2 mg/ml, 0.5 ml/kg) as well as aseptic treatment. Animals were mounted in a stereotaxic frame. To avoid a drop in body temperature a heat pad was used. To prevent animals from dehydration 2 ml of Ringer solution was subcutaneously injected every two hours.

Duratomy and craniotomy was done before the training started with a recovery period of one day before training. Dura mater was removed right above the prefrontal cortex. To limit growth tissue formation, Mitomycin (0.1 mg/ml in Saline, Sigma) was applied on brain surface for 10 min. Next a layer of paraffin wax and silicon (Kwik-Sil or Kwik-Cast, World Precision Instruments) was used to close the window in the skull and sealed with a plastic cap to protect brain until opened again for injection.

When rats were behaviourally ready, temporary inactivation of neuronal activity in the prelimbic cortex was achieved by a local injection of γ-aminobutyric acid ($GABA_A$) receptor agonist muscimol (Sigma Aldrich) using glass pipettes. Animals were anesthetised by 1.5% Isoflurane. For each animal the experiment consisted of 6 consecutive testing days. The fluids muscimol (0.125 µg/µl) and saline (0.9%) were administered alternating from day to day, starting with saline on the first day. Injection was performed using a Picospritzer III (Parker Hannifin, Precision Fluidics Division). After removing paraffin wax and silicon to lay open brain surface, pipette was placed at coordinates AP 3.2-3.5 mm, ML 0.5-0.7 mm and DV 2.5-2.7 mm. By observing the downward movement of the fluids meniscus in the pipette injection speed was controlled. When fluid was fully administered the pipette was left in place to allow the injected volume to diffuse into brain tissue. After removing the pipette, the skull

was closed again with paraffin wax and silicon. Behavioural testing started approximately 45 min after injection.

V.3. Statistics

To test statistical significance, multi-way-ANOVA followed by Bonferoni-post-hoc-test was used. To asses normality of sample sets Kolmogorov-Smirnov-test was used. In case of non-normal distributions the non-parametric Kruskal-Wallis-test followed by Bonferoni-post-hoc-test or Bonferoni-corrected sequential Mann-Whitney-U-test were used. Statistical significance levels were set to $p < 0.05$. All values are shown as mean ± SEM. Tests were performed using MATLAB® 2012b (the MathWorks, Inc., Natick, Massachusetts, United States).

V.4. Contributions

Rat handling and training for the decision confidence task was performed by the author, Anna Jelem. Task establishment and development was achieved by the author together with Michael Lagler. MATLAB scripts for training and statistics were provided by Michael Lagler.
The behavioural training of animals for the pharmacological inactivation of the medial prefrontal cortex (revision of Lagler et al. (2016))was performed by Anna Jelem, supported by Romana Hauer. Muscimol injections were performed by Michael Lagler. Behavioural observation during the experiment was under the responsibility of Anna Jelem.
All results and statistics were discussed and modelled by Anna Jelem and Michael Lagler.

VI.
Results
Decision confidence task

To study confidence in a perceptual decision making task, we used an auditory set-up, exposing the subjects to 50 Hz-Poisson-distributed click trains. Animals had to assess on which side of their head a higher number of clicks was presented. Most likely decisions were made based on evidence accumulation (Brunton et al., 2013; Lak et al., 2014; Sanders et al., 2016). Reward anticipation times were measured for correct choices by introducing catch trials (8%-18%) in which reward delivery was cut out. The data presented here is the result of a number of 9-68 training sessions. Each session had a varying amount of trials mostly between 500 and 1200. The data presented here derives from a chosen set of training days, depending on the animals' performances. The data used from rat ML105 is based on 12 data sessions, the data from ML106 is based on 68 data sessions, the data from ML118 is based on 9 data sessions and the data from ML124 is based on 33 data sessions.

VI.1. Learning

To achieve psychometric behaviour, expressing the animals' average performances over approximately 500-1200 trials, a daily training of 2 hours minimum was established. In the example of rat ML105, a training period of 23 days was necessary to reach a performance level where the animal showed neither a strong bias, nor a performance for high evidence trials lower than 80% choice accuracy (Fig. 11).

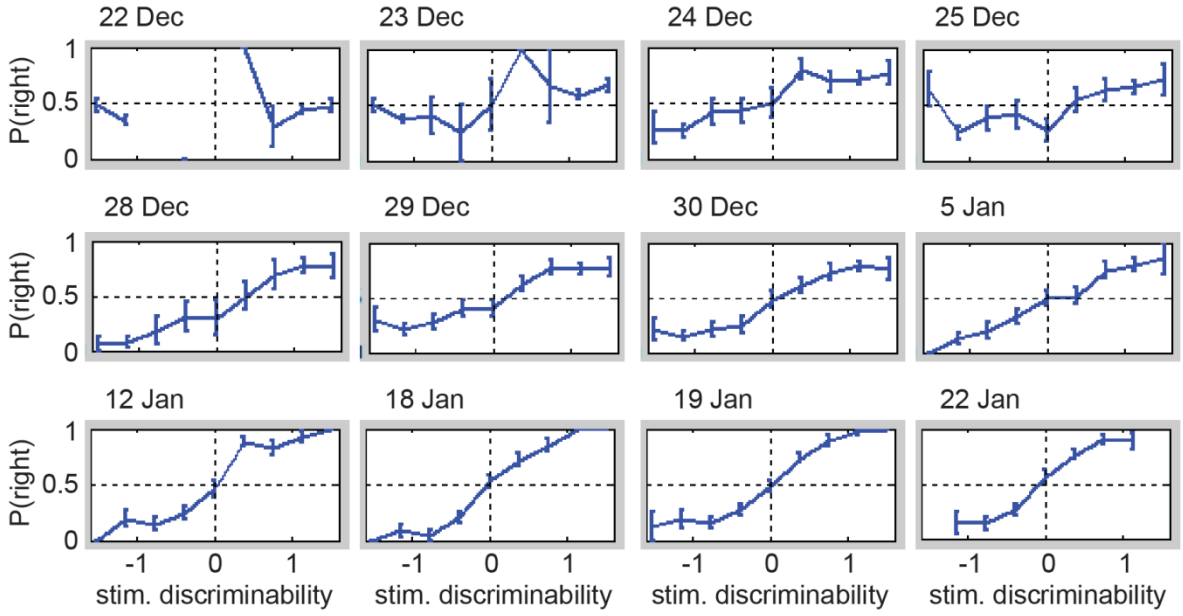

Fig. 11, Psychometric performance of individual sessions during training of the auditory click train discrimination task shown for rat ML105. Stimulus discriminability is shown as the log-ratio of the number of right and left clicks. P(right) indicates percentage of right choices.

VI.2. Stimulus integration and choice

An animal's ability to sample (listen to the click trains, staying in the centre port) long enough, is an important feature and must be gained during training. Sampling allows an animal to accumulate enough evidence for one or the other choice, resulting in a good performance. Our animals were all trained to sample for a period longer than ~320ms per trial. Pulling out too early resulted in an abortion of the trial, no reward and a punishment of a 2 second delay before a new trial could be initiated. Subjects ML105 and ML106 showed a mean sampling time of 0.35 seconds, while ML118 and ML124 showed a mean sampling time of 0.4 seconds (Fig. 12).

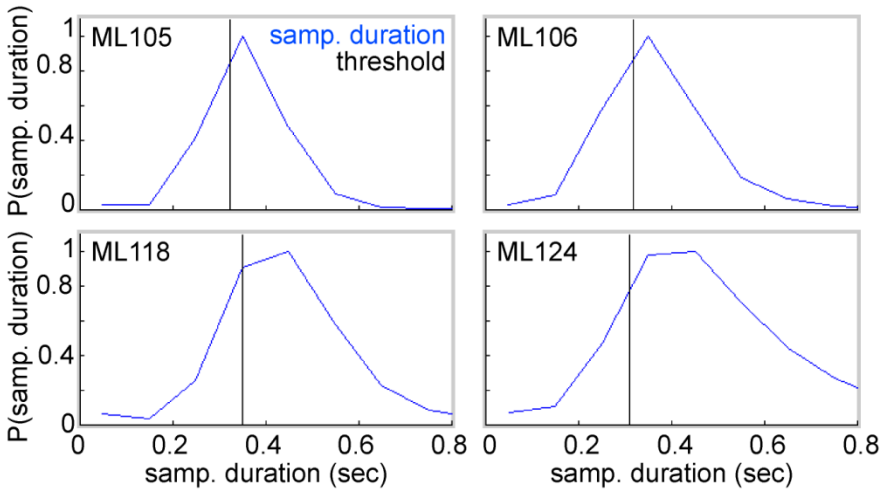

Fig. 12, Distributions of stimulus sampling times of all trials before pulling out of the centre port for rat ML105, ML106, ML118 and ML124. The mean-minimum-sampling threshold (black vertical line) indicates the time the animal has to stay at least in the centre port, listening to the stimulus. All trials in which the animal pulled out too early (area under the curve on the left side of the threshold) were unrewarded lost trials ending immediately after pull out.

Interestingly, all four animals had a very high likelihood of leaving the reward port before reward delivery for trials with lowest evidence discriminability (Fig 13). The probability of a dismissed reward at zero evidence level was 35% for ML105, 39% for ML106, 40% for ML118 and 37% for ML124, indicating strong uncertainty about these decisions. Looking at the subject's performance curves, we observed well developed psychometric functions depicting the animals' accuracies for right evidence trials (positive exponential) and left evidence trials (negative exponential). ML105, ML106, ML118 and ML124 had their performance-maxima for very easy right evidence trials with accuracies of 92%, 87%, 95% and 82% as well as accuracies of 95%, 92%, 91% and 91% for very easy left evidence trials. ML105 and ML124 had a 50% chance of making a correct decision in trials with an evidence discriminability of almost zero. ML106 and ML118 showed both a small side bias with accuracies of 52% and 55% for right evidence trials.

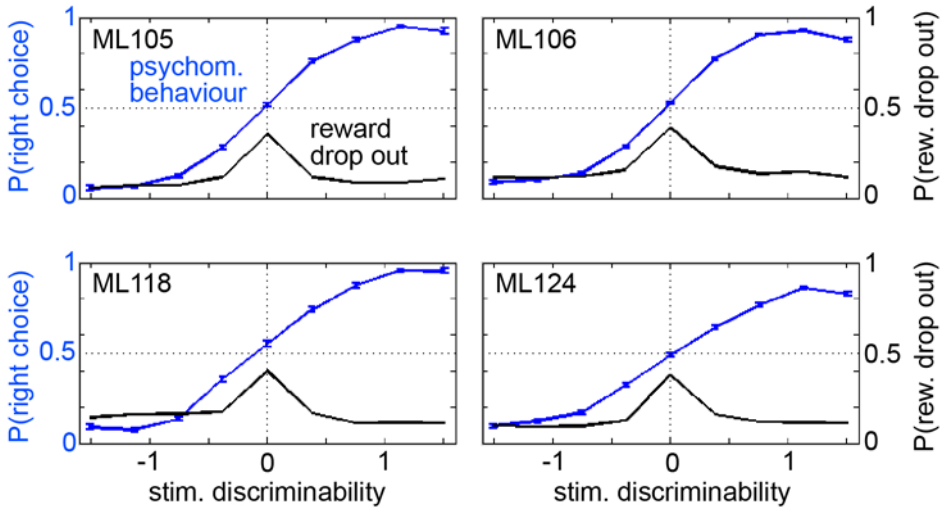

Fig. 13, Psychometric functions (blue curves) show animals' average accuracies (%) for trials with evidence for right choices across all evidence discriminability severities, calculated by the logarithm of the ratio between right and left click amount per trial, log(nClickright/nClickleft). In most difficult trials the discriminability between left and right is almost zero, whereas it is a higher positive value in very easy trials with evidence for right choice.
The black curves depict the animals' average likelihood to pull out of the reward ports before reward delivery. Note the peaks at highest difficulty, where evidence discriminability is the lowest.

Since evidence accumulation is the basis principal of this auditory click discriminability task, we aimed to plot evidence accumulation during particular case. For this, we took correct trials which had zero evidence by chance (n clicks left = n clicks right) due to the exact time point the animal left the centre port. It seems that click trains of zero evidence in total (no difference in click number) do carry decision triggering information. When following the ramping pattern of decision evidence for one or the other choice of rat ML105, it seems that rather than decision value itself, instead the steepness of the last evidence ramp might have caused the animal's choice (Fig. 14, top left).
In zero evidence trials with long reward anticipation times, accumulated evidence for the choice was much clearer than in those zero evidence trials in which reward anticipation times were short. In these trials of longer reward anticipation times, decision values stayed clearly off the midline and on the side of choice evidence for a period longer than 100 ms according to the animal's decision (Fig. 14, second and fourth column).

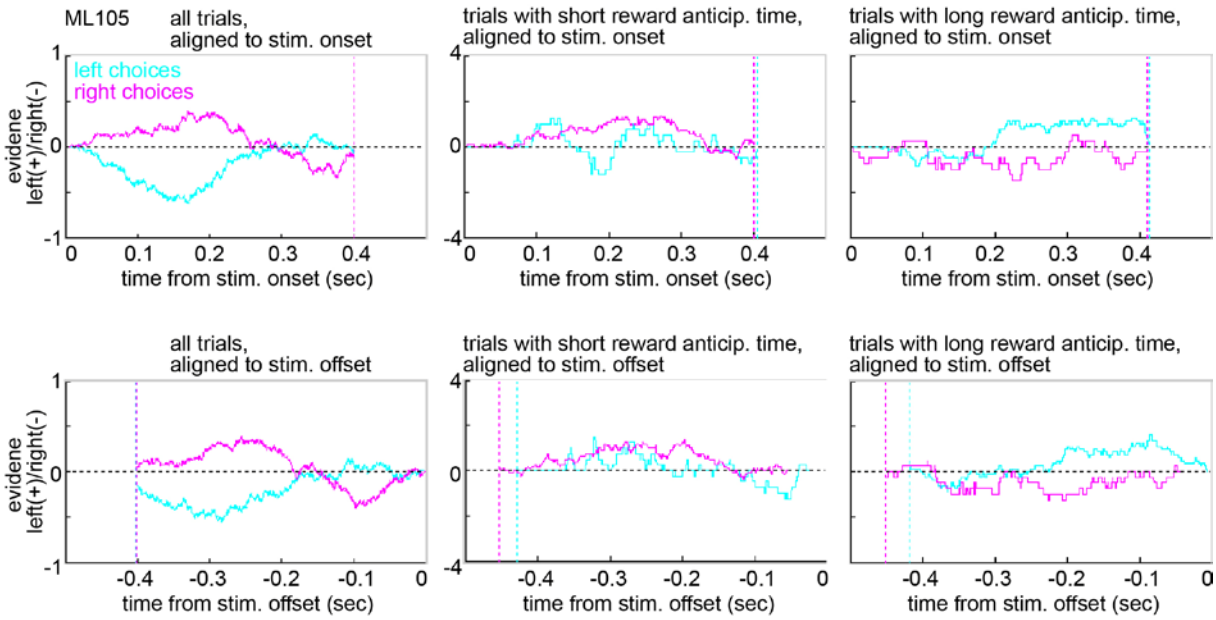

Fig. 14, Evidence accumulation based on click train generation shown for zero evidence trials. Depicted are all zero evidence trials (left column), short reward anticipation time trials (middle column) and long reward anticipation time trials (right column). All three evidence accumulation views are calculated for both, identical click train onset and identical click train end, separately, because the used data samples contain click trains of different lengths. Note that trials in which animals showed long reward anticipation times exhibit evidence accumulation values off the midline.

Furthermore, in non-zero evidence trials evidence is accumulating slowly for low stimulus discriminability trials and more quickly (steeper ramp) for high stimulus discriminability trials. However, in both cases evidence accumulation does not affect decision confidence (Fig. 15).

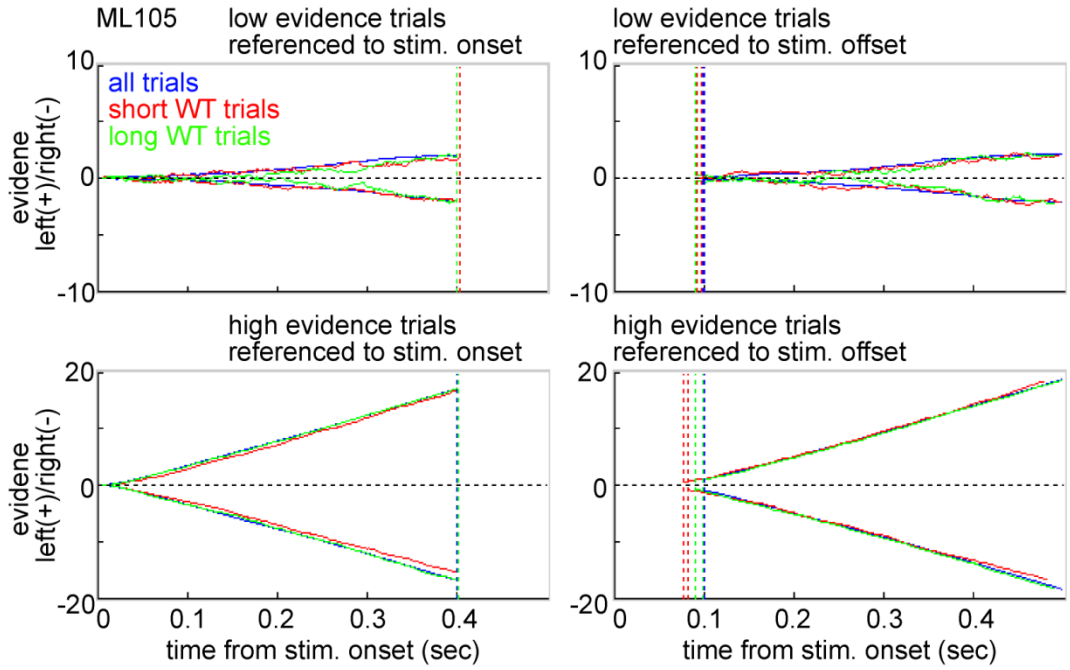

Fig. 15, Evidence integration based on Poisson click train generation. Shown are low evidence trials referenced to the stimulus onset (top left) as well as referenced to the stimulus offset (top right) and high evidence trials referenced to the stimulus onset (bottom left), high evidence trials referenced to the stimulus offset (bottom right).

VI. 3. Decision Confidence

Since the paradigm of this auditory post-decision-wagering task assumes that the animal's willingness to wait for reward was a direct read out for decision confidence, reward anticipation times were measured for all incorrect trials and correct catch trials for comparison. Our results show that all four animals exhibited significantly longer waiting times in correct catch trials (Fig. 16) compared to incorrect trials or correct trials, which stayed unrewarded due to pulling out before reward delivery. Mean waiting times for correct catch trials of ML105, ML106, ML118 and ML124 were 4.71, 4.29, 6.10 and 4.13 seconds. Mean values for incorrect trials were 4.22, 2.87, 5.17 and 3.7 seconds, respectively. Therefore, the average difference in time between correct catch and incorrect trials, which subjects spent in one of the reward ports anticipating water, was 0.49 seconds ($p < 0.001$, n Corr.catch = 631, n Error = 1853) in case of ML105, 1.42 seconds ($p < 0.001$, n Corr.catch = 2209, n Error = 7185) in case of ML106, 0.93 seconds ($p < 0.001$, n Corr.catch = 355, n Error = 1475) in case of ML118 and 0.43 seconds ($p < 0.001$, n Corr.catch = 341, n Error = 3770) in case of ML124. Notably, ML105 and ML106 had a significant number of incorrect trials with the same waiting time as for unrewarded correct trials. This could be explained by the assumption that during unrewarded correct trials animals were similarly uncertain as in incorrect trials, which was most likely caused by trial difficulty. For ML118 and ML124 we could not observe this pattern due to the high amount of trials in which the animals were pulling out earlier than the requested minimum anticipation time of 0.5 seconds.

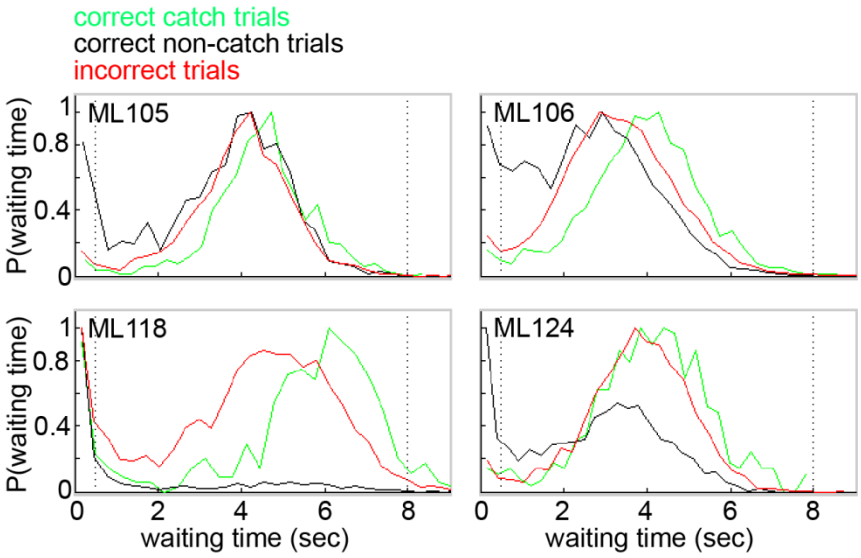

Fig. 16, Distributions of reward anticipation times in unrewarded trials. Waiting time in the reward ports for correct catch trials are depicted in green, incorrect trials are indicated by the red line and the black coloured curve shows correct non-catch trials in which the animals left the ports before reward was delivered. Note the clear right-shift of the distribution of correct catch trials for all animals. We performed a Kruskal-Wallis test to assess significance of the factor trial type (ML105: $p < 0.001$, $n = 3194$; ML106: $p < 0.001$, $n = 13108$; ML118: $p < 0.001$, $n = 2601$; ML124: $p < 0.001$, $n = 5597$). Using Bonferroni post hoc tests we tested the three anticipation time distributions for significant difference. For a complete description of statistical results see table 1.

Figure 17 is an example for one training session of approximately 900 trials. Shown are all waiting times of the four different trial types across stimulus discriminability according to the animal's behaviour.

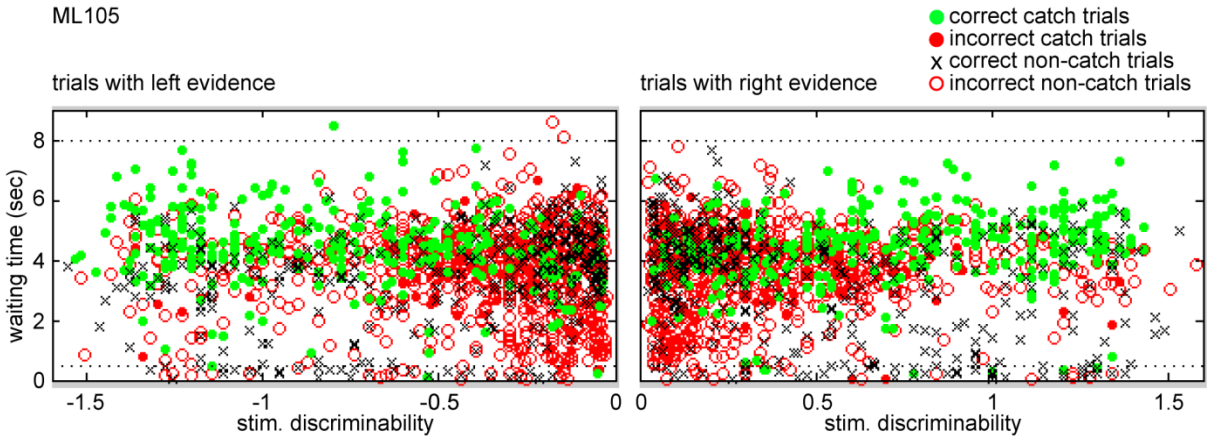

Fig. 17, Reward anticipation times for all completed non-rewarded trials for left and right choices across stimulus discriminability difficulties of the rat ML105 during an individual session. Green filled circles depict reward anticipation times for correct catch trials, in which no reward was given in order to measure the animal's maximum willingness to wait. Red filled circles depict incorrect catch trials. Red circles are incorrect-non-catch trials and black crosses show unrewarded correct trials (correct non-catch). Note that incorrect non-catch trials accumulate between the log ratio values 0 and -0.5 for left choices and 0 and 0.5 for right choices. Correct catch trials separate from incorrect catch trials being on average most present around 4 seconds of reward anticipation time. Difficult (-0.5 to 0 and 0 to 0.5) correct non-catch trials accumulate at 4 seconds as well, indicating the animal's maximum willingness to wait.

Having measured the reward anticipation times for correct catch and all incorrect trials across all trial difficulties, we are able to show a clear differentiation of waiting times in anticipation of reward based on correct and incorrect choices (Fig. 18). Taking reward anticipation times as read outs for decision confidence we observed that all four animals were more confident in correct easy trials compared to incorrect trials of same difficulty. In detail, for decisions based on highest evidence discriminability, subject ML105 was spending on average 4.72 seconds in the right and 4.66 seconds in the left reward port before initiating a new trial. For incorrect choices of highest evidence discriminability ML105 waited 3.47 seconds in the right and 3.6 seconds in the left port. This results in a time difference of 1.25 seconds ($p < 0.001$; n correct = 97, n error = 51) for right high evidence and 1.06 seconds ($p < 0.001$; n correct = 110, n error = 66) for left high evidence trials. For both, incorrect and correct choices, based on lowest evidence discriminability, ML105 was willing to wait a period of approximately 4 seconds. Similarly, ML124 showed an average anticipation time for easy correct right trials of 4.18 seconds and 4.08 seconds for easy correct left trials. When the animal's choice was incorrect, ML124 waited on average 3.35 seconds on the right and 3.57 seconds on the left side for easy trials. This results in a waiting time difference of 0.61 seconds ($p < 0.001$; n correct = 80, n error = 451) for right high evidence and 0.73 seconds ($p < 0.001$; n correct = 63, n error = 300) for left high evidence trials. Subjects ML106 and ML118 were clearly differentiated in waiting time for incorrect choices across difficulties but showed rather constant reward anticipation times for correct decisions. ML106 waited on average 2.84 seconds on the right and 2.93 seconds on the left side for incorrect trials of highest stimulus discriminability, while staying on average 3.48 seconds after most difficult decisions with negative outcome. Reward anticipation for correct choices we observed to be very uniform for easy right evidence trials and trials of lowest evidence discriminability with a waiting time of 3.86 seconds. For left correct choices the rat ML106 was willing to wait a bit longer, 4.24 seconds. Therefore, we calculated a time difference of 0.93 seconds ($p < 0.001$; n correct = 274, n error = 302) for easy right evidence trials, 1.4 seconds ($p < 0.001$; n correct = 276, n error = 339) for easy left evidence trials and additionally a difference of 20 milliseconds ($p < 0.001$; n correct = 580, n error = 4358) for trials of highest stimulus difficulty. Rat ML118 showed a clear drop in waiting time for incorrect trials of easiest difficulty, with 3.94 seconds

of reward anticipation for right evidence trials and 3.56 seconds for left evidence trials. The waiting time peak for incorrect trials was calculated to be 4.74 seconds on highest difficulty level. Measured times for correct right evidence trials of easiest difficulty were 5.84 seconds, for correct trials of lowest evidence discriminability it waited on average 5.54 seconds and for correct left evidence trials 5.42 seconds. This leads to a mean difference in waiting time of 1.48 seconds ($p < 0.001$; n correct = 54, n error = 33) for easy right evidence trials, 2.28 seconds ($p < 0.001$; n correct = 53, n error = 80) for easy left evidence trials and a difference of 80 milliseconds ($p < 0.01$; n correct = 69, n error = 820) for trials with lowest stimulus discriminability.

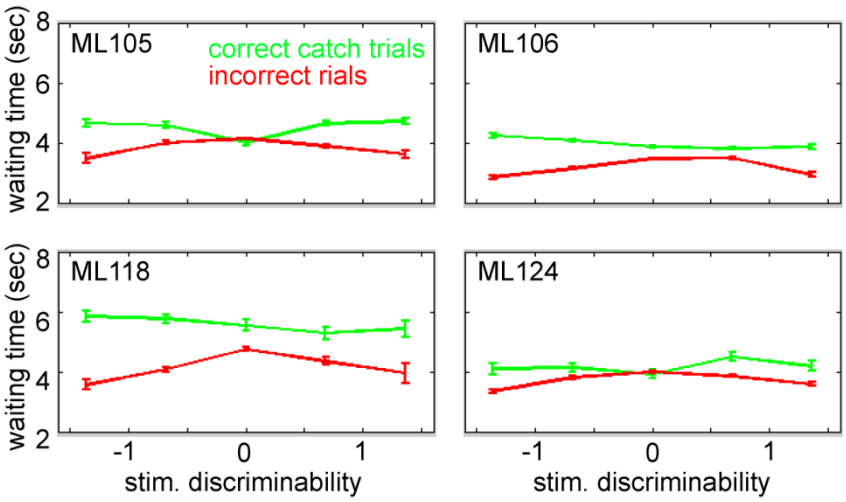

Fig. 18, Confidence report type 1. Time spent in reward ports is significantly longer for correct catch trials (green) than for incorrect trials (red). To investigate the impact of evidence and outcome on reward anticipation time, we performed a 2-way-ANOVA followed by Bonferroni post hoc tests. In case of trial outcome all 4 rats showed significantly longer reward anticipation times during correct than during incorrect choices (outcome factor: ML105: $p<0.001$, n = 2483; ML106: $p<0.001$, n = 9393; ML118: $p<0.001$, n = 1805; ML124: $p<0.001$, n = 4081). The separation between the two reward anticipation times appears broader at the edges, where stimulus discriminability becomes easier and is the widest at easiest discrimination (interaction of outcome and evidence: ML105: $p<0.001$; ML106: $p<0.001$; ML118: $p<0.001$; ML124: $p<0.001$; Bonferroni post hoc for high left evidence and high right evidence: ML105: $p<0.001$ (n = 110 correct and n = 66 error trials), $p<0.001$ (n = 97 correct and n = 51 error trials). To support this statistical procedure, we also performed a sequence of Bonferroni-corrected Mann-Whitney U-test. For a complete description of statistical results see table 2 and 3. All values are shown as mean ± SEM.

Furthermore, we could observe that the animals' reward anticipation times, which can be interpreted as levels of confidence, predict the subject's accuracy (Fig. 19). The longer the animals were willing to wait for reward, the more likely the choices were correct. According to that, we observed ML105, ML106, ML118 and ML124 having accuracies of 89%, 92%, 88% and 91% for maximum waiting time trials and accuracies of 59%, 68%, 64% and 52% for minimum waiting time trials (waiting time difference WT1, WT5: $p < 0.05$, n = 27, 71; $p < 0.001$, n = 238, 145; $p < 0.2345$, n = 9, 142; $p < 0.05$, n = 25, 23).

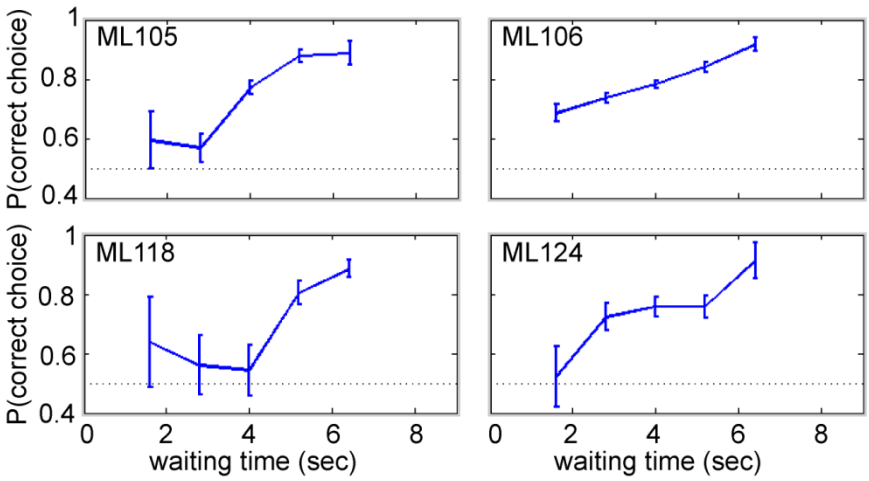

Fig.19, Confidence report type 2. Accuracy distributions of all completed trials across reward anticipation times (waiting time). Note the positive correlation between accuracy and the time the animals spent in the reward ports, anticipating water. For statistics, we performed a Kruskal-Wallis test to assess significance of the factor Waiting time (ML105: $p < 0.001$, $n = 775$; ML106: $p < 0.001$, $n = 2687$; ML118: $p < 0.001$, $n = 305$; ML124: $p < 0.05$, $n = 433$). To compare the different waiting time bins (WT1-WT5 from left to the right) a Bonferroni post hoc test was performed. For a complete description of statistical results see table 4 and 5. All values are shown as mean ± SEM.

Besides the fact that trial difficulty can be used for choice outcome prediction, adding the decision confidence (reward anticipation time) is further improving the accuracy prediction (Fig. 20). All animals showed higher accuracies for trials with longer reward anticipation times compared to trials with shorter reward anticipation times and this across all difficulties. Unfortunately, small trial numbers hindered results of the comparison between long and short waiting time trials from being significant. We could find a significant difference in accuracy for moderate difficulty (stim. discriminability 0.75) for ML105 ($p < 0.001$, n L.short.WT = 158, n L.long.WT = 199) and ML106 ($p < 0.01$, n L.short.WT = 617, n L.long.WT = 620), though.

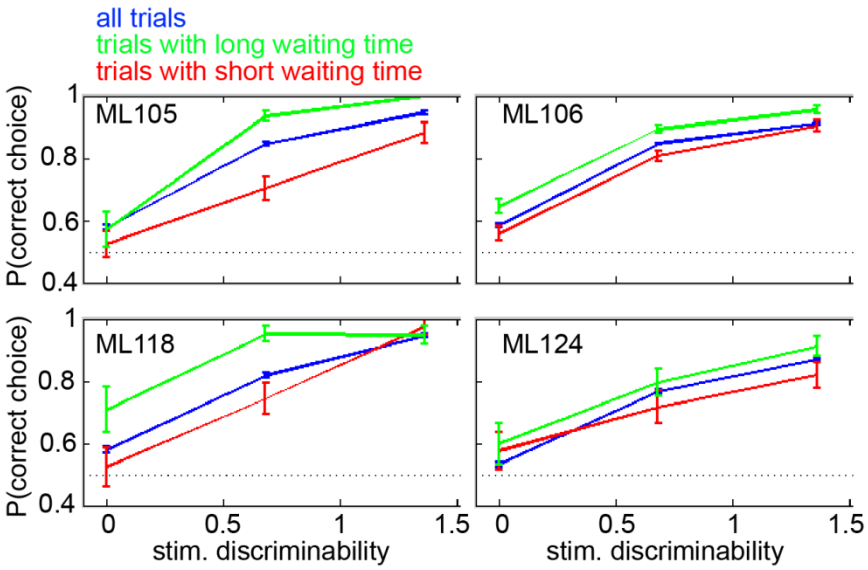

Fig. 20, Confidence report type 3. Reward anticipation times were split into long-waiting time trials (green) and short-waiting time trials (red) separated by the median of all anticipation times. Note that not only trial difficulty predicts the animals' accuracies but even reward anticipation times, interpreted as levels of confidence, improve trial outcome predictions. To assess the impact of stimulus discriminability (Factor Evidence: ML105: $p < 0.001$, $n = 9437$; ML106: $p < 0.001$, $n = 33792$; ML118: $p < 0.001$, $n = 6915$; ML124: $p < 0.001$, $n = 15576$) and confidence (Factor Waiting time: ML105: $p < 0.001$, $n = 9437$; ML106: $p < 0.001$, $n = 33792$; ML118: $p < 0.001$, $n = 6915$; ML124: $p < 0.2039$, $n = 15576$) on trial outcome a 2-way-ANOVA was performed. To test for separation of the three curves across stimulus discriminability we used the Bonferroni post hoc test, followed by a sequence of Bonferroni-corrected Mann-Whitney U-test. For a complete description of statistical results see table 6 to 9. All values are shown as mean ± SEM.

VI. 4. Reward and error updating

Reward and error updating are described by the animal's change in behaviour and choice for the upcoming decisions based on the experiences made in previous trials. Reward updating should take correct and error updating should take incorrect decisions in account. In general, it depicts the animal's flexibility and ability to learn. Regarding decision confidence, we were interested in how decision confidence and previous trial outcome, together, influence the animal's future decisions. Data from rat ML118 are shown here. We found, that in short waiting time trials, which are trials of low confidence (red curves), the animal had a clear bias towards the previously rewarded side (Interaction1, table 10: $p < 0.001$, $n = 9972$), while in trials of long waiting times, assumed as trials of high confidence (green curves), the rat's decision was unaffected by previous trial outcome (Fig. 21, top row, first and second column). When stimulus discriminability of a previous trial was low (high difficulty) but rewarded, ML118 showed a clear bias for this previously rewarded side (Interaction1, table 11: $p < 0.001$, $n = 9936$) in following trials with low confidence (Fig 21, top row, third and fourth column). Trials of low confidence (red curves) were strongly affected by previous trial evidence (Interaction1, table 11: $p < 0.001$, $n = 9936$), whereas in trials defined by high confidence (green curves), evidence of previously rewarded trials had no effect on choice behaviour (Fig. 21, top row, third and fourth column).

We did not observe any effect on behaviour concerning error updating. This might be because of the catch trials, incorrect trials and trials, in which the animal left before reward delivery, were all unrewarded (Fig. 21, bottom row). Hence, the animal could not receive any information about its previously incorrect decisions.

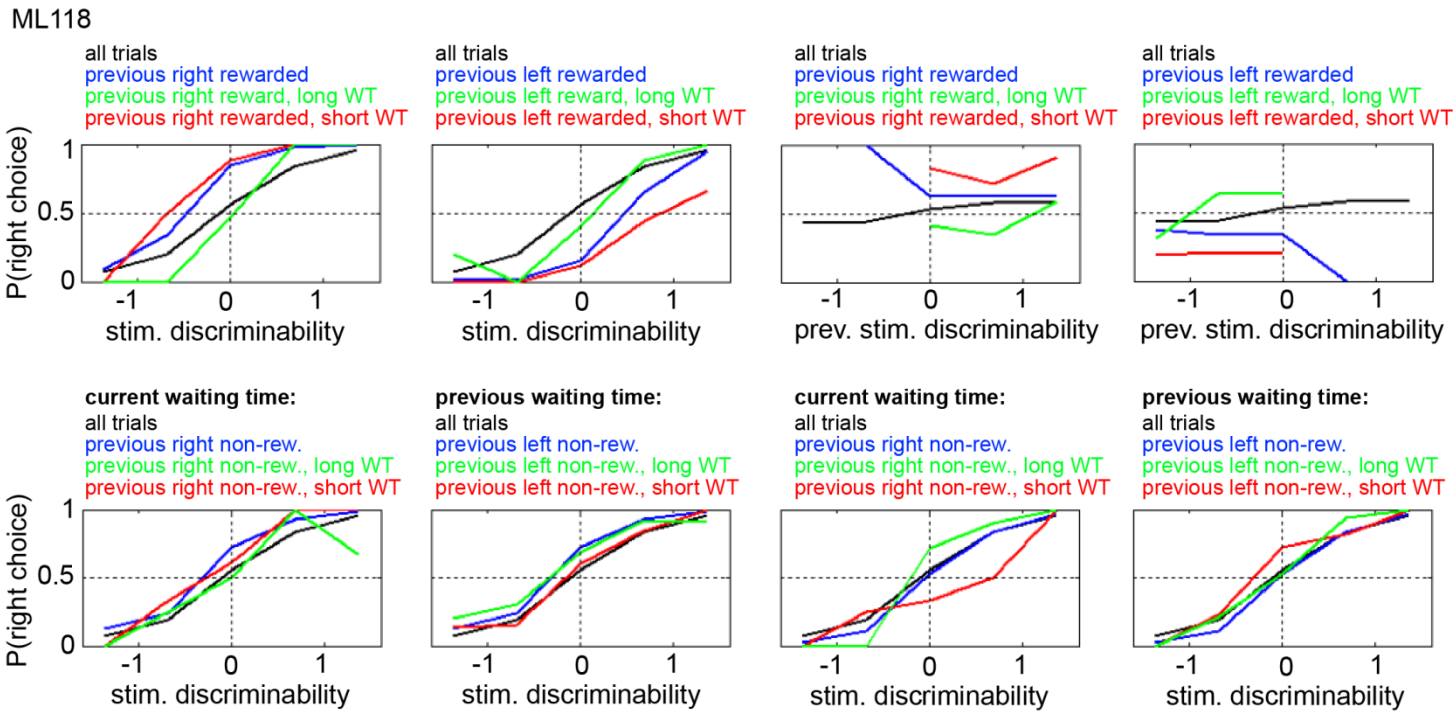

Fig. 21, top row, Reward updating behaviour of ML118 for previously right and previously left rewarded trials analysed for reward anticipation times (waiting times) of previous or current trials. To assess the impact of the factors Evidence (ML105: $p < 0.001$, $n = 13441$; ML106: $p < 0.001$, $n = 47455$; ML118: $p < 0.001$, $n = 9972$; ML124: $p < 0.001$, $n = 24112$), Outcome (ML105: $p < 0.001$, $n = 13441$; ML106: $p < 0.001$, $n = 47455$; ML118: $p < 0.001$, $n = 9972$; ML124: $p < 0.001$, $n = 24112$) and Waiting Time on current trial choice we performed a 3-way-ANOVA. Note the trend that confidence affected reward updating behaviour (factor Waiting time: no ANOVA test result due to too small n number). We observed significant test results of ANOVA interaction tests for all three factors (Evidence, Outcome, Waiting time), supporting the following observations: Psychometric behaviour was shifted towards the previously rewarded side (black curves include all trials, blue curves only trials that were previously rewarded). In detail, during trials with short reward anticipation times (red curves) the animal showed a strong bias towards the previously rewarded side. In trials, when the animal expressed high levels of confidence (green curves) no reward updating bias was present. Previous stimulus discriminability had a strong effect only on trials with low confidence (Interaction1, table 11: $p < 0.001$, $n = 9936$). For a complete description of statistical results see table 10 and 11.

Bottom row, The error updating behaviour of ML118 for previously unrewarded left and previously unrewarded right trials from the view of current or previous evidence. Data showed no effect of previously unrewarded trials.

VII.
Results
Medial prefrontal cortex inactivation

VII.1. Muscimol-inactivation of the medial prefrontal cortex in a working memory-guided decision making task

The working memory is needed for transient holding and processing of information. For a working memory project (Lagler et al., 2016), in which parvalbumin positive interneurons of the medial prefrontal cortex have been recorded, a control experiment using muscimol injections was performed. Four rats were trained to perform in a cue matching-to-place task. They learned to match two liquid stimuli with their specific reward locations on a Y-maze, with a 6 second-delay before choice execution. The animals went through 6 testing days in an alternating manner. On day 1 saline was injected into the medial prefrontal cortex of both hemispheres resulting in normal performance (~80%). The second day muscimol injection tremendously impaired performance decreasing it to 50% (by-chance-level). Muscimol wash-out by saline injection re-established performance. This pattern was observed for all four animals. By inactivation of the medial prefrontal cortex we could show that this region plays a crucial role for working memory. The animals' goal run durations were not impaired showing that the range of muscimol was restricted to working memory alone and did not affect other cognitive processes like goal-run behaviour or motor functions (Fig. 22).

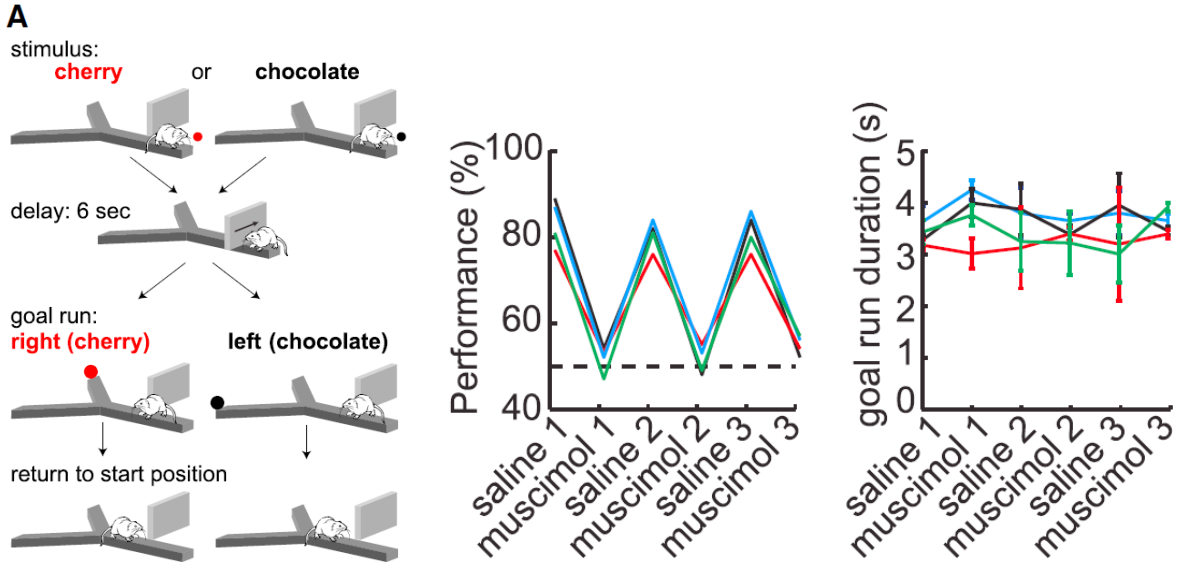

Figure 22, Delayed cue matching-to-place task (Lagler et al., 2016). Animals learned to associate a liquid flavour (chocolate or cherry) with a reward location on a Y-maze. After sampling, the animal's response was artificially delayed for 6 seconds by an automatically closing door. Muscimol injections into the medial prefrontal cortex reduced performances to chance-level (50% correctness). Notably, performance was restored on every other day when the control substance saline was injected. To support these findings statistically, we calculated the probability of this pattern occurring randomly as $p = 1/(20^4) = 0.00000625$, $n = 4$. Goal run duration remained unaffected.

VIII.
Discussion

VIII.1. Collapsing boundaries, stereo-clicks and future perspectives

To investigate decision confidence related neuronal activity in the orbitofrontal cortex of male Long-Evans rats we established an auditory two-alternative-post-decision-wagering task (Brunton et al., 2013; Lak et al., 2014; Sanders et al., 2016). In a period of 12 months we were able to gain expertise in animal training and optimised the task to an extend that allowed the animals to reach a high level of performance in click train differentiation. Furthermore we managed to receive confidence reporting reward anticipation times (Lak et al., 2014) using the benefits of catch trials. ML105, ML106, ML118 and ML124 reached our training goals and are ready for freely moving extracellular single cell recordings followed by juxtacellular labelling (Pinault, 1996).

Our results suggest that decision confidence may be reflected by the animals' willingness to wait for reward (Lak et al., 2014). Decision confidence or uncertainty (Kepecs et al., 2008) is directly linked to stimulus difficulty and expected decision outcome.

Underlining the stimulus evidence accumulation theory (Gold and Shadlen, 2007), we could show developing click accumulation across time for a sample of by-chance-zero evidence discriminability trials (Fig. 14). Interestingly, we observed a ramping of the mean decision value for the opposite direction, before gaining evidence for the animal's final decision. Therefore it seems that the process of evidence accumulation might follow the concept of random walk models (Gold and Shadlen, 2007), without stable decision boundaries but rather boundaries that collapse over time. The longer the subject listens, the less and less evidence is needed to trigger a decision. In other words, the more the boundaries converge over time, the more likely it is for the decision value to hit a boundary (Hawkins et al., 2015). Diffusion models fitting best to our observations would be the gradual collapse or the late collapse model (Hawkins et al., 2015).

Auditory perception and click differentiation play an essential role in our task. The brain has to detect when, on which side and how many clicks were presented. As previously described in the introduction, contrary to neurons of the primary visual cortex, cells of the primary auditory cortex are highly flexible and can change firing patterns as well as sensory representation (DeWees et al., 2005). In this process, not only excitation, but also inhibition plays an important role. Since our task provides fast click trains of a total frequency of 50Hz, the minimum mean inter-click-interval was approximately 20 milliseconds. Thus, the phenomena of auditory masking and auditory suppression (Fritz et al., 2005; Wehr and Zador, 2005) are crucial. In the rat primary auditory cortex click series of same frequencies might lead to forward suppression (Wehr and Zador, 2005). This means, if the first inter-click interval is≤ 128 milliseconds, the succeeding click is completely suppressed. However, neuronal activity recovers progressively for longer intervals (Wehr and Zador, 2005). In the case of our Poisson-click-discrimination task, forward suppression is more probable to happen, considering the minimum mean inter-click interval of 20 milliseconds. Since rats always try to find the most time- and best energy-efficient strategy to solve a task, a first-click strategy would be very likely. There are two reasons why the very first sensory input can strongly trigger and influence the decision of the animal. First, in trials of clear evidence discriminability, the first click strongly indicates the correct side. Second, the very first sensory input is assumed to be of high impact, enhanced by the expectation, attention and free cognitive capacity of the animal. Cognitive capacity describes the readily available pool of neurons excitable by auditory stimulation. Due to forward suppression the size of this pool gradually decreases with every input. Consequently, neuronal responses to auditory stimuli are progressively dampened.

To avoid a first-click strategy, click train presentations start with a stereo click. This stereo-click will recruit a random selection of neurons in the primary auditory cortex (DeWees et al., 2005).

A very similar precursor to our experiment was a two-alternative-odour-mixture-categorisation task (Kepecs et al., 2008) performed on Long-Evans rats. Animals had to take a sniff of an odour mixture

and decide which side to go based on the compound concentration. In this study, decision confidence and its related cell activity in the orbitofrontal cortex was recorded for the first time. The reason for using auditory click trains as stimuli is that it causes decision confidence to be developed over time by sampling the auditory cue and accumulating evidence. The circumstance that decisions evolve out of a "longer-lasting" process, in which evidence is constantly changing, creates a lot more uncertainty than sniffing, for which just one sample contains the entire information needed. By creating more uncertainty we expect neuronal activity related to decision confidence and uncertainty to be stronger. Also concerns about the orbitofrontal cortex processing only olfactory information rather than reflecting decision confidence could be diminished.
Interestingly, cells reacting due to uncertainty have already been described in rats before but in relation to spatial goals. Feierstein et al. (2006) recorded cells in the orbitofrontal cortex that were selectively firing for error trials in particular around the time point water would be delivered. Some other cells were firing with increased frequency during correct trials. These cells were referred to as outcome representative cells. Put in relation to decision confidence those cells could also represent uncertainty and confidence cells as described two years later (Kepecs et al., 2008).
The future goals of this project are to maintain and improve training to record single cells in the orbitofrontal cortex of freely moving rats. Juxtacellular labelling with glass electrodes (Pinault, 1995) will be performed to allow histological and immunological examination of the recorded cells.
Although the orbitofrontal cortex is causally linked to the expression of meta-cognition in the form of decision confidence (Lak et al., 2009), knowledge about the underlying circuitry is very limited. Neither do we know the targets confidence is broadcasted to, nor the local mechanisms responsible for generating such a signal. Therefore in the future, it will be important to identify projection routes as well as input specificities that are associated with distinct aspects of decision confidence. Further, investigating the cell-type specificity in contributing to the representation of confidence in the orbitofrontal cortex will be a crucial step. Finally, cell-type specific and precisely timed manipulation of the orbitofrontal circuitry will provide further insights into confidence.

VIII.2. Relevance of working memory in decision making

We assume that working memory forms the basis of higher cognitive processes including goal-directed decision making and metacognitive processing like decision confidence. This is underlined by other inactivation studies (Horst and Laubach, 2009; Urban et al., 2014) as well, demonstrating the importance of the working memory for decision making. Interestingly it could be shown that prelimbic cells, which were episode modulated along the delayed cue matching-to-place-paradigm, decreased their differential episode modulation strength when cue information was lost. Modulation was decreased even more when a choice intention was not permitted (Lagler et al., 2016). This indicates the existence of neurons in the medial prefrontal cortex which specifically support working memory function. Furthermore, episode modulation seems to be dependent on working memory. Thus, muscimol inactivation of the prelimbic cortex might inhibit neuronal representations of future choice (Fujisawa and Buzsáki, 2011), sequential episodes, as well as episode modulation (Lagler et al., 2016).

Appendix

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
16	ML105	Kruskal-Wallis	Trial type	3194	$3.0839e^{-25}$	***
		Bonferroni post hoc	Corr.catch vs. Error	631 1853	$2.8487e^{-19}$	***
			Corr.catch vs. Corr.n.catch	631 710	$1.1446e^{-22}$	***
			Error vs. Corr.n.catch	1853 710	0.0090	**
	ML106	Kruskal-Wallis	Trial type	13108	$9.6876e^{-202}$	***
		Bonferroni post hoc	Corr.catch vs. Error	2209 7185	$3.5082e^{-73}$	***
			Corr.catch vs. Corr.n.catch	2209 3714	$1.8281e^{-200}$	***
			Error vs. Corr.n.catch	7185 3718	$1.7190e^{-75}$	***
	ML118	Kruskal-Wallis	Trial type	2601	$1.4657e^{-37}$	***
		Bonferroni post hoc	Corr.catch vs. Error	355 1475	$1.1864e^{-27}$	***
			Corr.catch vs. Corr.n.catch	355 791	$1.9394e^{-35}$	***
			Error vs. Corr.n.catch	1475 791	$5.9028e^{-06}$	***
	ML124	Kruskal-Wallis	Trial type	5597	$1.2219e^{-61}$	***
		Bonferroni post hoc	Corr.catch vs. Error	341 3770	$8.3845e^{-05}$	***
			Corr.catch vs. Corr.n.catch	341 1486	$2.6299e^{-33}$	***
			Error vs. Corr.n.catch	3770 1486	$2.8595e^{-53}$	***

Table 1, Corr.catch = Correct catch trials, Error = incorrect non-catch trials + incorrect catch trials, Corr.n.catch = Correct non-catch trials

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
18	ML105	2-way-ANOVA	Evidence	2483	0.0229	*
			Outcome	2483	$1.0972e^{-25}$	***
			Interaction	2483	$1.2161e^{-12}$	***
		Bonferroni post hoc	LH.correct vs. LH.error	110 66	$2.6424e^{-09}$	***
			LL.correct vs. LL.error	147 319	$1.4754e^{-05}$	***
			Z.correct vs. Z.error	121 1108	1	n.s.
			RL.correct vs. RL.error	156 308	$4.7155e^{-10}$	***
			RH.correct vs. RH.error	97 51	1.7269^{-06}	***
		U-test	LH.correct vs. LH.error	110 66	$3.6278e^{-07}$	***
			LL.correct vs. LL.error	147 319	$1.3821e^{-07}$	***
			Z.correct vs. Z.error	121 1108	0.1912	n.s.
			RL.correct vs. RL.error	156 308	$6.5951e^{-13}$	***
			RH.correct vs. RH.error	97 51	$8.6611e^{-10}$	***
	ML106	2-way-ANOVA	Evidence	9393	$7.2345e^{-05}$	***
			Outcome	9393	$6.8326e^{-99}$	***
			Interaction	9393	$4.1094e^{-25}$	***
		Bonferroni post hoc	LH.correct vs. LH.error	276 339	$4.0392e^{-39}$	***
			LL.correct vs. LL.error	533 1291	$1.8067e^{-43}$	***
			Z.correct vs. Z.error	580 4358	$4.7839e^{-10}$	***
			RL.correct vs. RL.error	546 894	$1.2929e^{-04}$	***
			RH.correct vs. RH.error	274 302	$1.5287e^{-16}$	***
		U-test	LH.correct vs. LH.error	276 339	$9.3770e^{-30}$	***
			LL.correct vs. LL.error	533 1291	$3.3482e^{-41}$	***
			Z.correct vs. Z.error	580 4358	$1.8620e^{-08}$	***
			RL.correct vs. RL.error	546 894	$2.8385e^{-08}$	***
			RH.correct vs. RH.error	274 302	$1.6511e^{-16}$	***

Table 2, LH.correct = Left-High-evididence-correct, LL.correct = Left-Low-evidence-correct, RH.correct = Reft-High-evididence-correct, RL.correct = Reft-Low-evidence-correct, LH.error = Left-High-evididence-error, LL.error = Left-Low-evidence-error, RH.error = Reft-High-evididence-error, RL.error = Reft-Low-evidence-error, Z.correct = Zero-evidence-correct, Z.error = Zero-evidence-error

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
18	ML118	2-way-ANOVA	Evidence	1805	0.0218	*
			Outcome	1805	$2.0682e^{-29}$	***
			Interaction	1805	$6.2205e^{-04}$	***
		Bonferroni post hoc	LH.correct vs. LH.error	53 80	$1.5298e^{-12}$	***
			LL.correct vs. LL.error	79 304	$6.7202e^{-12}$	***
			Z.correct vs. Z.error	69 820	0.0015	**
			RL.correct vs. RL.error	78 235	$6.6553e^{-04}$	***
			RH.correct vs. RH.error	54 33	0.0419	*
		U-test	LH.correct vs. LH.error	53 80	$9.0219e^{-14}$	***
			LL.correct vs. LL.error	79 304	$1.7855e^{-13}$	***
			Z.correct vs. Z.error	69 820	$3.8005e^{-06}$	***
			RL.correct vs. RL.error	78 235	$9.3243e^{-06}$	***
			RH.correct vs. RH.error	54 33	$8.2157e^{-04}$	***
	ML124	2-way-ANOVA	Evidence	4081	0.0019	**
			Outcome	4081	$2.9076e^{-11}$	***
			Interaction	4081	$4.4127e^{-04}$	***
		Bonferroni post hoc	LH.correct vs. LH.error	63 300	$2.5519e^{-04}$	***
			LL.correct vs. LL.error	64 593	1	n.s.
			Z.correct vs. Z.error	72 1624	1	n.s.
			RL.correct vs. RL.error	61 773	0.0013	**
			RH.correct vs. RH.error	80 451	$9.5336e^{-04}$	***
		U-test	LH.correct vs. LH.error	63 300	$1.7375e^{-05}$	***
			LL.correct vs. LL.error	64 593	0.264	n.s.
			Z.correct vs. Z.error	72 1624	0.6717	n.s.
			RL.correct vs. RL.error	61 773	$6.9209e^{-04}$	***
			RH.correct vs. RH.error	80 451	$5.4308e^{-04}$	***

Table 3, LH.correct = Left-High-evididence-correct, LL.correct = Left-Low-evidence-correct, RH.correct = Reft-High-evididence-correct, RL.correct = Reft-Low-evidence-correct, LH.error = Left-High-evididence-error, LL.error = Left-Low-evidence-error, RH.error = Reft-High-evididence-error, RL.error = Reft-Low-evidence-error, Z.correct = Zero-evidence-correct, Z.error = Zero-evidence-error

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
19	ML105	Kruskal-Wallis	Waiting time	775	$2.1484e^{-10}$	
		Bonferroni post hoc	WT1 vs. WT2	27 104	1	n.s.
			WT1 vs. WT3	27 336	0.3140	n.s.
			WT1 vs. WT4	27 237	0.0070	**
			WT1 vs. WT5	27 71	0.0164	*
			WT2 vs. WT3	104 336	$1.1855e^{-04}$	***
			WT2 vs. WT4	104 237	$1.8694e^{-09}$	***
			WT2 vs. WT5	104 71	$5.1627e^{-06}$	***
			WT3 vs. WT4	336 237	0.0236	*
			WT3 vs. WT5	336 71	0.3125	n.s.
			WT4 vs. WT5	237 71	1	n.s.
	ML106	Kruskal-Wallis	Waiting time	2687	$7.8164e^{-10}$	
		Bonferroni post hoc	WT1 vs. WT2	238 667	1	n.s.
			WT1 vs. WT3	238 1051	0.0092	**
			WT1 vs. WT4	238 586	$1.0802e^{-05}$	***
			WT1 vs. WT5	238 145	9.1076^{-07}	***
			WT2 vs. WT3	667 1051	0.2163	n.s.
			WT2 vs. WT4	667 586	$9.5619e^{-05}$	***
			WT2 vs. WT5	667 145	$1.6800e^{-05}$	***
			WT3 vs. WT4	1051 586	0.0790	n.s.
			WT3 vs. WT5	1051 145	0.0024	**
			WT4 vs. WT5	586 145	0.4254	n.s.

Table 4, WT (1-5) = Waiting time from left to the right

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
19	ML118	Kruskal-Wallis	Waiting time	305	$1.7154e^{-04}$	***
		Bonferroni post hoc	WT1 vs. WT2	9 22	1	n.s.
			WT1 vs. WT3	9 38	1	n.s.
			WT1 vs. WT4	9 94	1	n.s.
			WT1 vs. WT5	9 142	0.2345	n.s.
			WT2 vs. WT3	22 38	1	n.s.
			WT2 vs. WT4	22 94	0.9590	n.s.
			WT2 vs. WT5	22 142	0.0245	*
			WT3 vs. WT4	38 94	0.6116	n.s.
			WT3 vs. WT5	38 142	0.0030	**
			WT4 vs. WT5	94 142	0.2418	n.s.
	ML124	Kruskal-Wallis	Waiting time	433	0.0329	*
		Bonferroni post hoc	WT1 vs. WT2	25 101	0.3784	n.s.
			WT1 vs. WT3	25 165	0.1133	n.s.
			WT1 vs. WT4	25 119	0.1401	n.s.
			WT1 vs. WT5	25 23	0.0186	*
			WT2 vs. WT3	101 165	1	n.s.
			WT2 vs. WT4	101 119	1	n.s.
			WT2 vs. WT5	101 23	0.5956	n.s.
			WT3 vs. WT4	165 119	1	n.s.
			WT3 vs. WT5	165 23	1	n.s.
			WT4 vs. WT5	119 23	1	n.s.

Table 5, WT (1-5) = Waiting time from left to the right

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
20	ML105	2-way-ANOVA	Evidence	9437	$3.6898e^{-54}$	***
			Waiting time	9437	$5.7009e^{-06}$	***
			Interaction	9437	0.0784	n.s.
		Bonferroni post hoc	Z.all vs. Z.short.WT	2562 145	1	n.s.
			Z.all vs. Z.long.WT	2562 77	1	n.s.
			Z.short.WT vs. Z.long.WT	145 77	1	n.s.
			L.all vs. L.short.WT	3915 158	$1.4422e^{-04}$	***
			L.all vs. L.long.WT	3915 199	0.0402	*
			L.short.WT vs. L.long.WT	158 199	$3.5743e^{-07}$	***
			H.all vs. H.short.WT	2166 94	1	n.s.
			H.all vs. H.long.WT	2166 121	1	n.s.
			H.short.WT vs. H.long.WT	94 121	0.9008	n.s.
		U-test	Z.all vs. Z.short.WT	2562 145	0.2115	n.s.
			Z.all vs. Z.long.WT	2562 77	0.9239	n.s.
			Z.short.WT vs. Z.long.WT	145 77	0.5027	n.s.
			L.all vs. L.short.WT	3915 158	$1.8553e^{-06}$	***
			L.all vs. L.long.WT	3915 199	$5.4404e^{-04}$	***
			L.short.WT vs. L.long.WT	158 199	$5.9813e^{-09}$	***
			H.all vs. H.short.WT	2166 94	0.0097	n.s.
			H.all vs. H.long.WT	2166 121	0.0087	n.s.
			H.short.WT vs. H.long.WT	94 121	$1.1756e^{-04}$	***

Table 6, Z.all = Zero evidence all trials, L.all = Low evidence all trials, H.all = High evidence all trials, Z.short.WT = Zero evidence short waiting time trials, Z.long.WT = Zero evidence long waiting time trials, L.short.WT = Low evidence short waiting time trials, L.long.WT = Low evidence long waiting time trials, H.short.WT = High evidence short waiting time trials, H.long.WT = High evidence long waiting time trials

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
20	ML106	2-way-ANOVA	Evidence	33792	$9.4709e^{-152}$	***
			Waiting time	33792	$2.3041e^{-06}$	***
			Interaction	33792	0.8108	
		Bonferroni post hoc	Z.all vs. Z.short.WT	10073 502	1	n.s.
			Z.all vs. Z.long.WT	10073 440	0.0455	*
			Z.short.WT vs. Z.long.WT	502 440	0.0233	*
			L.all vs. L.short.WT	13754 617	0.5482	n.s.
			L.all vs. L.long.WT	13754 620	0.1282	n.s.
			L.short.WT vs. L.long.WT	617 620	0.0041	**
			H.all vs. H.short.WT	7211 258	1	n.s.
			H.all vs. H.long.WT	7211 317	1	n.s.
			H.short.WT vs. H.long.WT	258 317	1	n.s.
		U-test	Z.all vs. Z.short.WT	10073 502	0.2514	n.s.
			Z.all vs. Z.long.WT	10073 440	0.01	n.s.
			Z.short.WT vs. Z.long.WT	502 440	0.0062	n.s.
			L.all vs. L.short.WT	13754 617	0.0083	n.s.
			L.all vs. L.long.WT	13754 620	0.0014	**
			L.short.WT vs. L.long.WT	617 620	$2.0505e^{-05}$	***
			H.all vs. H.short.WT	7211 258	0.6517	n.s.
			H.all vs. H.long.WT	7211 317	0.0058	n.s.
			H.short.WT vs. H.long.WT	258 317	0.0125	n.s.

Table 7, Z.all = Zero evidence all trials, L.all = Low evidence all trials, H.all = High evidence all trials, Z.short.WT = Zero evidence short waiting time trials, Z.long.WT = Zero evidence long waiting time trials, L.short.WT = Low evidence short waiting time trials, L.long.WT = Low evidence long waiting time trials, H.short.WT = High evidence short waiting time trials, H.long.WT = High evidence long waiting time trials

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
20	ML118	2-way-ANOVA	Evidence	6915	$2.2809e^{-17}$	***
			Waiting time	6915	$3.5174e^{-04}$	***
			Interaction	6915	0.2589	n.s.
		Bonferroni post hoc	Z.all vs. Z.short.WT	1887 60	1	n.s.
			Z.all vs. Z.long.WT	1887 40	0.0487	*
			Z.short.WT vs. Z.long.WT	60 40	0.0196	*
			L.all vs. L.short.WT	2819 77	1	n.s.
			L.all vs. L.long.WT	2819 81	0.295	n.s.
			L.short.WT vs. L.long.WT	77 81	0.36	n.s.
			H.all vs. H.short.WT	1856 39	1	n.s.
			H.all vs. H.long.WT	1856 56	1	n.s.
			H.short.WT vs. H.long.WT	39 56	1	n.s.
		U-test	Z.all vs. Z.short.WT	1887 60	0.2445	n.s.
			Z.all vs. Z.long.WT	1887 40	0.0115	n.s.
			Z.short.WT vs. Z.long.WT	60 40	0.0061	n.s.
			L.all vs. L.short.WT	2819 77	0.3370	n.s.
			L.all vs. L.long.WT	2819 81	0.0083	n.s.
			L.short.WT vs. L.long.WT	77 81	0.0054	n.s.
			H.all vs. H.short.WT	1856 39	0.6796	n.s.
			H.all vs. H.long.WT	1856 56	0.4354	n.s.
			H.short.WT vs. H.long.WT	39 56	0.3841	n.s.

Table 8, Z.all = Zero evidence all trials, L.all = Low evidence all trials, H.all = High evidence all trials, Z.short.WT = Zero evidence short waiting time trials, Z.long.WT = Zero evidence long waiting time trials, L.short.WT = Low evidence short waiting time trials, L.long.WT = Low evidence long waiting time trials, H.short.WT = High evidence short waiting time trials, H.long.WT = High evidence long waiting time trials

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
20	ML124	2-way-ANOVA	Evidence	15576	$2.9268e^{-18}$	
			Waiting time	15576	0.2039	
			Interaction	15576	0.6186	
		Bonferroni post hoc	Z.all vs. Z.short.WT	3532 66	1	n.s.
			Z.all vs. Z.long.WT	3532 55	1	n.s.
			Z.short.WT vs. Z.long.WT	66 55	1	n.s.
			L.all vs. L.short.WT	5805 74	1	n.s.
			L.all vs. L.long.WT	5805 88	1	n.s.
			L.short.WT vs. L.long.WT	74 88	1	n.s.
			H.all vs. H.short.WT	5793 83	1	n.s.
			H.all vs. H.long.WT	5793 80	1	n.s.
			H.short.WT vs. H.long.WT	83 80	1	n.s.
		U-test	Z.all vs. Z.short.WT	3532 66	0.4803	n.s.
			Z.all vs. Z.long.WT	3532 55	0.3159	n.s.
			Z.short.WT vs. Z.long.WT	66 55	0.7906	n.s.
			L.all vs. L.short.WT	5805 74	0.3165	n.s.
			L.all vs. L.long.WT	5805 88	0.5155	n.s.
			L.short.WT vs. L.long.WT	74 88	0.2423	n.s.
			H.all vs. H.short.WT	5793 83	0.1700	n.s.
			H.all vs. H.long.WT	5793 80	0.2643	n.s.
			H.short.WT vs. H.long.WT	83 80	0.0831	n.s.

Table 9, Z.all = Zero evidence all trials, L.all = Low evidence all trials, H.all = High evidence all trials, Z.short.WT = Zero evidence short waiting time trials, Z.long.WT = Zero evidence long waiting time trials, L.short.WT = Low evidence short waiting time trials, L.long.WT = Low evidence long waiting time trials, H.short.WT = High evidence short waiting time trials, H.long.WT = High evidence long waiting time trials

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
21	ML105	3-way-ANOVA	Evidence	13441	$3.0169e^{-114}$	***
			Outcome	13441	$1.0587e^{-16}$	***
			Waiting time	13441	NeT	
			Interaction 1	13441	$2.9079e^{-10}$	***
			Interaction 2	13441	$7.3488e^{-08}$	***
			Interaction 3	13441	$6.7686e^{-05}$	***
	ML106	3-way-ANOVA	Evidence	47455	$1.1881e^{-294}$	***
			Outcome	47455	$7.5430e^{-50}$	***
			Waiting time	47455	NeT	
			Interaction 1	47455	$4.6953e^{-50}$	***
			Interaction 2	47455	$7.5710e^{-05}$	***
			Interaction 3	47455	$4.6010e^{-17}$	***
	ML118	3-way-ANOVA	Evidence	9972	$3.3244e^{-50}$	***
			Outcome	9972	$1.3908e^{-06}$	***
			Waiting time	9972	NeT	
			Interaction 1	9972	$2.8269e^{-70}$	***
			Interaction 2	9972	0.5738	n.s.
			Interaction 3	9972	$3.6028e^{-05}$	***
	ML124	3-way-ANOVA	Evidence	24112	$1.2e^{-45}$	***
			Outcome	24112	$2.4643e^{-06}$	***
			Waiting time	24112	NeT	
			Interaction 1	24112	$4.145e^{-35}$	***
			Interaction 2	24112	0.8733	n.s.
			Interaction 3	24112	0.0725	n.s.

Table 10, Evidence = Stimulus discriminability, Interaction 1 = Evidence x Outcome, Interaction 2 = Evidence x Waiting time, Interaction 3 = Waiting time x Outcome, NeT = not enough trials

Fig.	Rat ID	Test	Factors	n	p-Value	Significance
21	ML105	3-way-ANOVA	Prev.Evidence	13409	0.9635	n.s.
			Outcome	13409	NeT	
			Waiting time	13409	NeT	
			Interaction 1	13409	$5.8571e^{-04}$	***
			Interaction 2	13409	0.9758	n.s.
			Interaction 3	13409	0.365	n.s.
	ML106	3-way-ANOVA	Prev.Evidence	47397	0.5674	n.s.
			Outcome	47397	NeT	
			Waiting time	47397	NeT	
			Interaction 1	47397	$1.1605e^{-06}$	***
			Interaction 2	47397	0.5564	n.s.
			Interaction 3	47397	$9.3129e^{-04}$	***
	ML118	3-way-ANOVA	Prev.Evidence	9936	0.7913	n.s.
			Outcome	9936	NeT	
			Waiting time	9936	NeT	
			Interaction 1	9936	0.0010	**
			Interaction 2	9936	0.2815	n.s.
			Interaction 3	9936	0.0046	**
	ML124	3-way-ANOVA	Prev.Evidence	24109	0.1369	n.s.
			Outcome	24109	NeT	
			Waiting time	24109	NeT	
			Interaction 1	24109	$9.7046e^{-06}$	***
			Interaction 2	24109	0.5824	n.s.
			Interaction 3	24109	0.3687	n.s.

Table 11, Previ.Evidence = Evidence of previous trial, Interaction 1 = Evidence x Outcome, Interaction 2 = Evidence x Waiting time, Interaction 3 = Waiting time x Outcome, NeT = not enough trials

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