3.1 General information about project C02

3.1.1 Project title: Exploratory attentional resource allocation by the anterior prefrontal cortex

3.1.2 Research area: Cognitive Neuroscience, Systemic Neuroscience, Neurophysiology

3.1.3 Principal investigators

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Is the employment of the project leader(s) at the institution(s) indicated contractually fixed for the duration of the proposed funding period? **yes**
Do any of the above mentioned persons hold fixed-term positions? **yes, Happel**
End date of fixed-term contract: **31/12/2021**
Further employment is guaranteed by host institution until the **end of the funding period.**
Funding for the project leader(s) at the institution(s) indicated is covered by core support (state funds or similar): **yes**

3.1.4 Legal issues

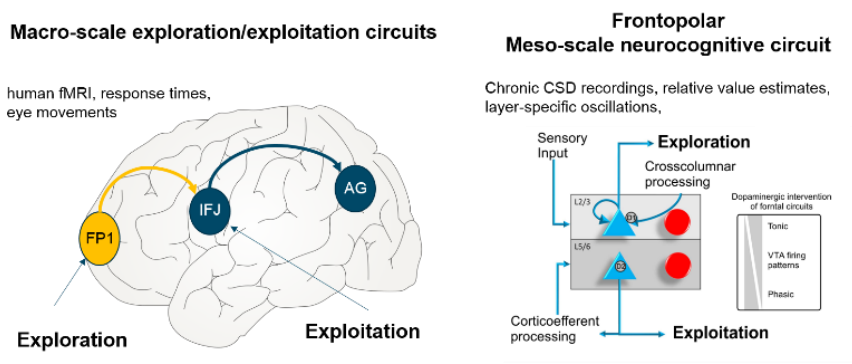
This project includes

1.	Research on human subjects or human material.	yes
	A copy of the required approval of the responsible ethics committee is included with the proposal.	yes
2.	Clinical trials.	no
3.	Experiments involving vertebrates.	yes
4.	Experiments involving recombinant DNA.	no
5.	Research involving human embryonic stem cells.	no
6.	Research concerning the Convention on Biological Diversity.	no
7.	Investigations involving dual use research of concern.	no

3.2 Summary

Allocation of attention enables us to focus on the task at hand. However, in a constantly changing environment it is also necessary to explore the environment for the adaptive reallocation of resources. The anterior prefrontal cortex (aPFC) is regarded as a decisive part of a neurocognitive circuit for the neuronal realization of exploratory resource allocation in human and non-human primates. However, rodents (with their less differentiated frontal cortex) also show exploratory resource allocation. We plan to investigate the neural processes of exploratory attentional resource shifts on the macro-scale and meso-scale across humans and Mongolian gerbils. We utilize a novel, complementary foraging paradigm in both species based on exploitation / exploration trade-offs and record brain activity from the aPFC with respect to its local micro- and widespread macro-circuitry. Moreover, there is emerging evidence that exploratory attention is diminished in old age revealed by—sometimes perseverative—exploitative behaviour. Exploratory resource allocation is also likely to be a prerequisite for successful transfer of learning. This will be investigated in collaboration with other subprojects of the CRC.

3.3 Research rationale



Schematic overview. *Left*, Schematic illustration of the involved brain regions during exploration-exploitation trade-offs. *Right*, Neuro-cognitive frontopolar circuit during attentional resource allocation and dopaminergic intervention by stimulation of the ventral tegmental area.

3.3.1 Current state of research and preliminary work

Imagine a Mongolian gerbil that forages a desert habitat for distributed food patches. When these patches become exhausted, the gerbil is in an exploitation/exploration dilemma: Should it exploit the current patch further or should it explore an alternative patch, suffering travel costs but enjoying potentially higher food density (Shuai and Song, 2011)?

Such a foraging example shows a fundamental resource allocation problem. The patch-leaving decision needs to be made based on probabilistic information (how much food is usually available in the alternative patch?) and in a potentially changing environment. This exploration/exploitation trade-off has been investigated in many animal species as well as humans. Patch-leaving behaviour is typically guided by the marginal value theorem (MVT; Constantino and Daw, 2015): the current patch is abandoned if the food capture rate (i.e. the time or effort needed to obtain a food item) drops to the average capture rate in a patch. All species from insects, to birds, to mammals and humans obey the MVT suggesting a fundamental underlying behavioural and potentially also neural mechanism. Exploration can be influenced by factors like the travel costs to a new patch and the predictability of food (Lottem et al., 2018). In humans, exploratory resource allocation has been shown to enable adaptation to continuous subtle changes of reward with high efficiency, e.g. in gambling situations (Daw et al., 2006; Raja Beharelle et al., 2015), attentional adaptations to environmental changes (Müller, et al., 1995; Chetverikov et al., 2017), or (analogous to foraging patterns in animal studies) in human visual search (e.g. Kristjansson et al., 2014, Wolfe et al., 2019).

We plan to use a complementary foraging paradigm to investigate neural circuits for exploratory attentional resource allocation across species. Accumulating evidence suggests that the human anterior prefrontal cortex (aPFC) plays a decisive role for the provision of exploratory resource allocation. The frontopolar cortex (FPC) was activated during exploratory decisions in gambling (Daw et al., 2006) and reflected the relative advantage in favour of switching to a foregone alternative action (Boorman et al, 2009). Frontopolar transcranial direct current stimulation modulated exploratory behaviour positively by anodal (excitatory) and negatively by cathodal (inhibitory) stimulation (Raja Beharelle et al., 2015). Anterior prefrontal lesions including the frontopolar cortex impaired the extrapolation of the most recent trend, although learning from past rewards was generally intact (Kovach et al., 2012).

In addition to human studies, aPFC lesions in monkeys showed increased persistence and reduced distractibility in the following of task rules. **An intact aPFC therefore contributes to a neurocognitive circuit that allows subject to disengage resources from the current task in order to explore alternative sources of reward in the environment** (Mansouri et al., 2015). Ample evidence suggests that rodents also show exploratory resource allocation (Karlsson et al., 2012; Kvitsiani et al., 2013). However, while primate aPFC has a causal role for exploratory attention shifts, the role of rodent frontal cortex is still debated (Burke et al., 1985; Olton et al., 1988; Karlsson et al., 2012). Human BA10 is characterised by high spine density but low cell body density, suggesting a role in information integration (Ramnani & Owen, 2004). One goal of this project is the delineation of commonalities and differences of exploratory resource allocation in species with and without a distinct BA10-like architecture.

An important commonality of all the primate studies is that switching behaviour per se was neither affected by aPFC lesions nor did it lead to aPFC activation. This distinguishes aPFC from more posterior parts of lateral prefrontal cortex, in particular the inferior frontal junction area (IFJ), that are commonly activated during switches between task sets (Brass et al., 2005). The aPFC (specifically frontopolar area FP1) and IFJ were coactivated in a meta-analysis of functional imaging studies (Bludau et al., 2015) which would be expected if aPFC modulates switching processes in IFJ to achieve exploratory attention shifts. Frontopolar area FP1 is characterised by a complex dendritic/spine system providing an excellent architecture for the integration of inputs (Jacobs et al., 2001) which would be a suitable neurocognitive

circuit for the comparison of current task aspects with novel information required for exploratory decisions. We are interested in investigating the neural circuits of this decision process as a fundamental neural resource by combining complementary research in human and rodent frontal cortices.
Finally, we plan to investigate the **potentially compromised exploratory resource allocation in the elderly**. Mata et al. (2009, 2013) observed detrimental perseveration of exploitation in foraging tasks, potentially due to a decrease in novelty pursuit with age (Düzel et al., 2010). We will test the hidden potential of frontopolar processing capacities altered in old age as a modulator of cognitive training success.

Own preliminary work:
Human studies*:* Early on, we observed **aPFC activation in fMRI studies investigating attentional resource allocation** between visual dimensions (such as colour and motion) in singleton search tasks in which the odd-one-out target was defined in varying feature dimensions like colour or motion direction (Pollmann et al., 2000, Weidner et al. 2002). Crucially, we observed aPFC activation during attention changes that were adaptive - moving attention to the current target-defining dimension - without being required by the task. Thus, the activation followed an **exploratory attention pattern**. A comparable pattern of frontopolar activation was also observed for attentional reorienting in space following invalid spatial cues (Lepsien and Pollmann 2002), demonstrating that aPFC was involved in resource allocation for both featural and spatial attention. Furthermore, patients with aPFC lesions showed a selective deficit in visual dimension weighting, demonstrating that the aPFC activations were not an epiphenomenon, but aPFC has a vital role in attentional resource allocation (Pollmann et al., 2007). In a recent study, we used a modified foraging paradigm and observed increased FPC activation when switches between two target types were freely chosen by the participants, in contrast to imposed switches (Fig. 1 Ort et al. 2019). These (and other, e.g. Konishi et al., 2005) **human studies demonstrated a role of FPC for the exploratory reallocation of attentional resources in striking agreement with the pattern observed in monkeys** (Pollmann, 2016).

Fig. 1. Activation elicited by freely chosen versus imposed switches in a modified foraging paradigm (after Ort et al., 2019). The red circle shows aPFC activation, the blue circle IFJ activation. Importantly, no FPC, but IFJ activation was observed for imposed switches versus no switches (not shown), indicating the specificity of FPC activation by freely chosen switches.

Note that these attention changes and the concomitant aPFC activation occurred in the absence of task rules that would dictate such changes. In fact, they often appeared to occur rather implicitly, in the absence of conscious deliberation. We could show anterior prefrontal involvement in implicit exploratory resource allocation using the contextual cueing paradigm, in which repeated presentation of the same spatial configuration of target and distractors leads to implicit learning and improved search guidance for these repeated configurations. After these repeated configurations were learned, we moved the target to a new place in the search display, requiring relearning of the implicitly learned configurations. We observed aPFC activation during these changes of implicitly learned target-distractor configurations, demonstrating that **aPFC supports implicit resource allocation processes** (Pollmann and Manginelli, 2009a,b). **Implicit resource allocation processes are ideally suited to investigate the underlying neuronal circuit mechanisms on the level of invasive animal experiments**, as planned in this proposal. Furthermore, we have shown that the human dopaminergic system is involved in processing a wide range of implicit and explicit rewards (reviewed by Daniel and Pollmann, 2014). One of the goals of the present project will be to investigate the modulatory role of dopamine for exploratory resource allocation across species.

Animal studies: To investigate the physiology of frontal pole cortex during attentional resource allocation on the micro- and meso-scale, we will use chronic *in vivo* recordings in the Mongolian gerbil (*Meriones unguiculatus*) to complement the macroscopic human investigation. We have developed chronic laminar multichannel recordings and analysis of the current source density (CSD) distribution in awake, behaving gerbils (Happel et al., 2015; Deane et al., 2019). The reference-free CSD distribution is derived from the laminar local field potential (LFP) and reveals the spatiotemporal sequence of neural activation across cortical layers as ensembles of synaptic population activity with high spatial and temporal precision (Happel et al., 2010). The CSD thus provides a functional readout of the cortical micro-circuitry function, encompassing a wider, meso-scopic field of view than single-unit and calcium-imaging based cell recording approaches (Buzsáki et al., 2012). For the primary auditory cortex, CSD analysis revealed task-dependent differences of the columnar activation patterns (cf. Fig. 2A).
According to reinforcement learning theories, goal-directed behaviour requires the estimation of the reward expected from a particular stimulus or action. Such value estimates can be identified by the

prediction error: the difference between expected reward and reward actually obtained (Schultz, 2015). We have recently applied reinforcement learning models and regression analysis to layer-wise CSD data in order to identify a relative value representation within the auditory cortex during a discrimination task (Fig. 2B; in collaboration with Prof. Gerhard Jocham, Univ. of Düsseldorf). With comparable behavioural modelling and regression methods, we plan to analyse **value representations during a foraging task in frontal human fMRI and animal *in vivo* physiological data sets** (cf. Hayden et al., 2012; Lottem et al., 2018). We suppose that a **transient decision variable and a decrease in such relative value estimation would reflect a neural resource of the needed change towards exploration** of other foraging sites (cf. Fig. 2B; Klein et al., 2017).

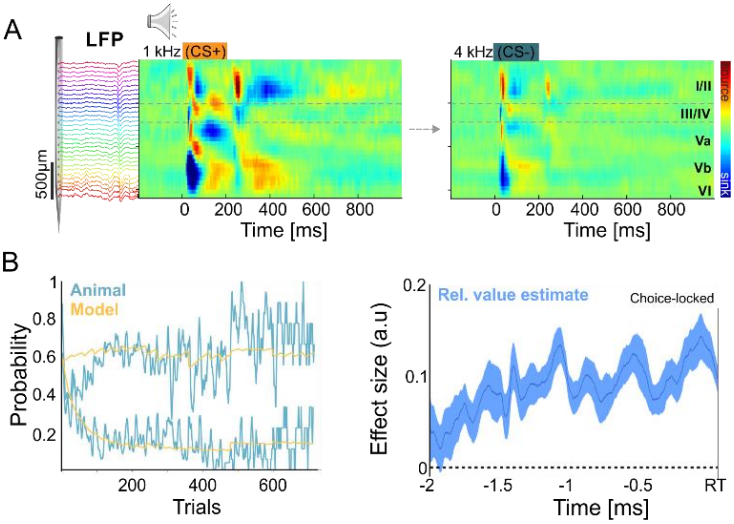


Fig. 2. Chronic CSD recording from the auditory cortex of Mongolian gerbils. A. We find task-dependent activation of the cortical micro-circuitry in response to the contingency of a presented pure tone frequency during an auditory discrimination task (CS+ vs. CS-). Cortical layers are indicated by Roman numbers. **B**. *Left*, Using reinforcement learning models (relative value Q-learning algorithm) and, *right*, regressed trial-by-trial neuronal data against the model predictions using multiple linear regression (cf. Klein et al., 2017; in collaboration with Prof. Gerhard Jocham, University of Düsseldorf). We could thereby detect a relative value estimate in the signal of the auditory cortex, which aligns with the choice of the animal.

Such reward-coding in the brain is based on reinforcement-evaluating brain structures, like the ventral tegmental area (VTA), which convey information about stimulus salience and valence to target areas distributed throughout the brain including frontal cortex (Bromberg-Martin et al., 2010). Frontal dopamine release originating from VTA projections is, indeed, a key correlate of encoding success or uncertainty in the brain—interpreted as a teaching signal (Schultz, 2015; Happel, 2016). **The animal research in this proposal allows to directly investigate how the neuromodulator dopamine codes for incentive choices during foraging behaviour and affects the frontal physiology (Salamone et al., 2005; Beeler et al., 2012).** Dopamine might bias decisions toward options with larger uncertainty, which has been interpreted as exploratory search strategy (Dezza et al., 2017; Cinotti et al., 2019). Recently, we established an optogenetic stimulation of VTA projection neurons in order to investigate its impact on cortical processing (Fig. 4B). We could reveal that reward-related modulation of auditory signal processing in the auditory cortex is relayed via a gain modulation of thalamic inputs in infragranular layers Vb/VIa (Brunk et al., 2019), which subsequently promote strengthened cross-columnar corticocortical processing (Happel et al., 2014; Deliano et al., 2018). Similarly, dopaminergic modulation of frontal layer-specific processing modes may set ground for the neural resource to code the salient representation of behaviourally-relevant stimuli (Homma et al., 2017; Brunk et al., 2019). Thereby, **frontal dopamine might mediate the trade-off between exploitation and exploration strategies based on the accumulation of task- and choice-related evidence via distinct micro-circuit processing modes** (Happel, 2016)—a hypothesis we investigate during foraging behaviour in the Mongolian gerbil.

To sum up, we will investigate the macro-circuits and micro-circuits underlying resource allocation in FP1 in humans and the rodent aPFC analogue. The complementary design of foraging tasks requiring attentional resource allocation in both species will allow us to integrate our findings from global and local neural realisations of exploratory attentional resource allocation into a common functional framework. Finally, we will use training interventions in the elderly to investigate the hidden potential of frontal circuit processing capacities for exploratory resource allocation as a modulator of training success.

3.3.2 Project-related publications by participating researchers

1. Brunk MGK, Deane KE, Kisse M, Deliano M, Vieweg S, Ohl FW, Lippert MT, **Happel MFK** (2019) Optogenetic stimulation of the VTA modulates a frequency-specific gain of thalamocortical inputs in infragranular layers of the auditory cortex. **Sci Rep** 9, 20385, doi:10.1038/s41598-019-56926-6
2. Deliano M, Brunk MGK, El-Tabbal M, Zempeltzi MM, **Happel MFK**, Ohl FW (2018) Dopaminergic neuromodulation of high gamma stimulus phase-locking in gerbil primary auditory cortex mediated by D1/D5-receptors. **Eur J Neurosci.** doi:10.1111/ejn.13898.

3. Homma N, **Happel MFK**, Nodal FR, Ohl FW, King AJ, Bajo VM (2017) A Role for Auditory Corticothalamic Feedback in the Perception of Complex Sounds. **J Neurosci** 37(25):6149-6161.
4. **Happel MFK** (2016) Dopaminergic impact on local and global cortical circuit processing during learning. **Behav Brain Res** 299:32–41.
5. **Happel MFK**, Deliano M, Handschuh J, Ohl FW (2014) Dopamine-modulated recurrent corticoefferent feedback in primary sensory cortex promotes detection of behaviorally relevant stimuli. **J Neurosci** 34:1234–1247.
6. Ort E, Fahrenfort JJ, Reeder R, **Pollmann S**, Olivers CNL (2019) Frontal cortex differentiates between free and imposed target selection in multiple-target search. **Neuroimage**, 202:116133.
7. **Pollmann S** (2016) Frontopolar Resource Allocation in Human and Nonhuman Primates. **Trends Cogn Sci** 20:84–86.
8. **Pollmann S (Ed.)**, Neuromethods: Spatial learning and attention guidance. **Springer**: New York. 1st ed. 2020, 320 p. ISBN 978-1-4939-9947-7.
9. Preuschhof C, Sharifian F, Rosenblum L, Pohl TM, **Pollmann S** (2019) Contextual cueing in older adults: Slow initial learning but flexible use of distractor configurations. **Vis Cognit**, https://doi.org/10.1080/13506285.2019.1668516.
10. Wang L, Baumgartner F, Kaule F, Hanke M & **Pollmann S** (2019). Individual face- and house-related eye movement patterns distinctively activate FFA and PPA. **Nat Commun**, **10,** 5532. doi:10.1038/s41467-019-13541-3

3.4 Project plan

The literature, including our own previous work, showcases the important role of the frontopolar cortex as a neurocognitive circuit for exploratory resource allocation. We here aim to understand the underlying functional mechanisms of frontopolar processing on the macro-scale and meso-scale across species.

3.4.1 Goals/Research questions

Can we infer common circuit processing mechanisms in aPFC across species during exploratory resource allocation (WP1.1+1.2/2.1+2.2)? How does human FPC interact with other supramodal areas? And how is exploratory resource allocation achieved on the meso-scale (WP1.4/2.3)? Is FPC-guided exploratory resource allocation reduced in the elderly brain (WP1.3/2.1)? Is it related to reduced frontopolar processing capacities and does this modulate training success (WP1.3/2.1)? Does an intervention in the neuromodulatory dopamine system impact on the neuronal processing modes in frontal cortex underlying flexible exploratory resource allocation as a potentially suitable target unleashing a hidden potential to compensate, for instance, for age losses (WP2.4)? Is this paralleled by activity changes in dopaminergic areas of the human brain (WP1.1-2)? These are the questions that we aim to address with this project, by integrating research across human and animal species with a common foraging task.

3.4.2 Work programme/Work packages

Work package 1 (human studies):
WP 1.1 A probabilistic foraging task to investigate exploration/exploitation behaviour
We will use a foraging task **closely analogous to the gerbil foraging task** in WP2.1 to investigate exploratory behaviour in humans. Participants will need to search for target items among distractors in a visual search task (Fig. 3). Distractor-target and distractor-distractor similarity will be chosen so that search becomes inefficient. We will use eye-movements as response and gaze-contingent display changes as feedback. Whenever a target has been fixated for 300 ms, it will briefly turn into a reward indicator which then returns to its previous appearance. This is the feedback that the target has been "foraged" and a reward has been received and search for the next target in the display can start. The more targets have been foraged in a display, the fewer targets remain. When a previous target is re-fixated, no reward feedback will appear and no reward will be earned. Participants can choose at any time to end the search in a display and to proceed to the next display with the full number of targets (patch leaving). However, before the next display is presented, a waiting time is inserted, analogous to patch leaving costs in ecological foraging or the movement from one foraging spout to the other in our gerbil experiment (WP2.1). If all targets in a display are foraged, the display will disappear and, after the waiting period, the next display will be presented.
In a fraction of the displays, presentation will terminate after the first few targets have been foraged, forcing the participant to abandon search and wait for the next display. This is a control condition for the assessment of involuntary switching, which should not depend on anterior PFC, but should activate more posterior brain areas, particularly the IFJ and the inferior parietal lobule, jointly with exploratory switches (Ort et al., 2019).

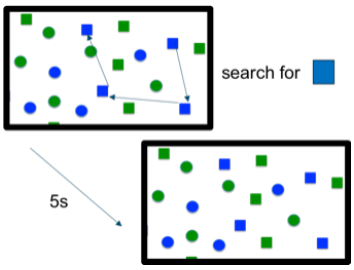


Fig. 3: A sample display. Participants search for one specific form-colour target, e.g. the blue squares (changed interindividually). One display will contain 20 items of each kind (In the figure, the number of targets is reduced for clarity). A target is selected by fixating it for 300 ms. It then turns to a "" for 500 ms to indicate 1 cent reward earned, before changing back to a blue square. Search can be ended at any time by pressing a button, and the display will disappear and a fixation cross will appear for 5 s (waiting time) before the next display appears and the search can continue. Parameters may be adapted in pilot experiments to obtain patch leaving after "foraging" ca. 50 % of targets in a display. Search will continue for the fixed duration of 20 min., so that patch leaving will not lead to a reduction of the amount of reward that can be earned over the whole experiment. In this time, ca. 100 displays can be searched, leading to an estimated average reward of 10 Cent / display x 100= 10 €, paid in addition to the fixed participant payment.

Search behaviour will be segmented into intertarget episodes, i.e. the times from one target fixation to the next (Kristjansson et al., 2019). These intertarget times (ITT) will inform us about search difficulty, which will increase with ongoing foraging in a display. Search within a display will be judged as exploitative behaviour, whereas the decision to end search and proceed to the next display ("patch leaving") will indicate the timepoint of the exploratory decision. However, decisions are often the consequence of a continuous build-up of evidence, e.g. as modelled by random walk models (Gold & Shadlen, 2007). To assess this accumulation process, we will calculate a deconvolution analysis of the BOLD signal covering the time period before the decision to leave the display (cf. Ort et al., 2019). Comparably, we will investigate this process of accumulating evidence with the same methods on a layer-specific level based on *in vivo* CSD data obtained in WP2.1. Whole brain imaging will also enable us to investigate reward-related activation changes in dopaminergic structures, particularly prediction errors, in parallel with gerbil work in WP2.4

FMRI data will be acquired using a 3 Tesla Philips Achieva dStream MRI scanner with a 32 channel head coil, using a T2*-weighted single-shot gradient echo-planar images sequence with 35 axial slices parallel to AC-PC, 3 mm isotropic voxels, FOV = 240 mm x 240 mm, inter-slice gap of 10 %, whole-brain coverage, TR = 2 s, TE = 30 ms, flip angle = 90°, parallel acquisition with sensitivity encoding (SENSE) with reduction factor 2. Structural images will be acquired using a T1-weighted (T1w) MPRAGE sequence with 192 slices, 1 mm isotropic voxels, FOV = 256 mm x 256 mm, TR = 9.7 ms, TE = 4.7 ms, inversion time = 900 ms, flip angle = 8°. Eye movements will be recorded during scanning with the EyeLink 1000 remote eye-tracking system at a sampling rate of 1000 Hz. For the measurement protocol, see Hanke et al. (2019). For gaze-contingent display change methods, see Ort et al. (2019). Sample size will be n=25 young participants. **Expected results**: We expect FPC activation to ramp up before patch-leaving decisions, whereas IFJ activation is expected when attention is switched from one target to the next within a display. We also expect prediction-error-associated activation in Ncl accumbens and putamen (Daniel and Pollmann, 2014),

WP1.2 Exploration of variable reward contingencies

While patch-leaving in experiment WP1.1 occurs in a predictable situation (the depletion of targets during search in a display), exploration can also be induced by changing payoffs of alternative choices (Daw et al. 2006; Raja Beharelle et al. 2015). In WP1.2, we will **induce exploratory behaviour by unpredictably changing the reward probability** of two target types that are simultaneously presented in a display. Similar displays as in WP1.1 will be used, but now two colour-form combinations could be chosen to serve as targets, e.g. the blue circles and the green squares. Reward feedback will also be given in the same way as in WP1.1, but now the first fixated target type (e.g. blue circle) will start with p=0.80 reward probability that after a pseudorandom number (between 5-10) of target fixations is reduced to p=0.20 until the other target is fixated. The new target type fixations are then rewarded with p=0.80, and the cycle starts again. To not confound target type switching with target depletion (patch leaving), we will present only two targets among 10 distractors in each visual search display. As soon as one target is selected by fixation, the display disappears and a central fixation cross is presented for 1s before the next display appears. In one half of the displays each, the targets will be of the same type (e.g. two blue circles) or of different types (blue circle and green square). Exploratory behavior will be operationalised as voluntary switches of the target type between successive two-type displays. Forced switches between successive target types (with analogous reward probabilities as in free switches) in the single target-type displays will serve as a non-exploratory switch-control condition. Typically, participants search preferentially the high reward targets (Wolfe et al., 2018). However, when the reward probability drops, exploratory switches to the other target type should follow (Daw et al., 2006; Raja Beharelle et al., 2015). **Expected results**: As in WP1.1, we expect aPFC activation to accompany and precede exploratory switches. In addition, we expect that aPFC activation patterns will represent the direction of switch (from target type a to b and v.v.) in keeping with recent data from our lab (Güldener et al., 2019). **This would confirm that aPFC actually processes the alternative options to choose from and not merely represents exploratory vs. exploitative action**. WP2.2 will investigate effects

of reward probabilities changes on exploration in the Mongolian gerbil on the meso-scopic synaptic circuit level. Measurement methods are the same as in WP1.1

WP1.3 Exploration/exploitation balance in the elderly
We will use the foraging paradigm from WP1.1 to investigate **if exploratory attention is reduced in the elderly - indicated by late patch leaving - with the potential exception of SuperAgers**. In related paradigms, reduced exploratory behaviour has been observed in elderly participants (Mata et al., 2009; 2013). We will investigate a sample of SuperAgers and an age-matched control group (n=20/group) to investigate foraging behaviour and relate it to structural changes in aPFC, specifically thickness of PFC (7T-MRI) as well as tau-pathology, which is known to affect aPFC early on. Furthermore, we will assess if rostral cingulate atrophy, respectively its absence in SuperAgers (along with higher density of von Economo neurons, Gefen et al., 2015), will be correlated with non-exploratory attention switching (Weidner et al., 2002).
In collaboration with **B05-Hopf/Schönfeld**, we will test in samples of n=20 young respectively elderly participants if the **attentional cycling between features tested in B05 will be modulated by interindividual differences in exploratory capacity and underlying aPFC processes**. **Expected results**: We hypothesise that a bias towards exploitation will go along with decreased attentional between-feature cycling in B05. Moreover, we hypothesise that intact exploration is a prerequisite for successful transfer of training - whereas a dominant exploitation bias may lead to faster skill acquisition within tasks. This will be tested in collaboration with B02 and B05.

WP1.4 Micro-circuits within FP1
The aPFC (FP1) differs from more posterior frontal cortices in the high complexity of its dendritic/spine system and is therefore in a unique position to integrate neuronal input (Jacobs et al., 2001; Yuste & Denk, 1995). We hypothesise that the dense connectivity of the supragranular FP1-layers may be essential for the role of FP1 in exploratory attention changes (Fig. 1, *right*). We know from our previous work that FP1 is specifically activated during exploratory changes. Here, we will use layer-specific fMRI with support from **Z02**-Kühn/Speck/Hanke to investigate if supragranular layers give rise to this activation (cf. WP2.3 for details; n=20). Furthermore, ongoing work shows that the alternative features to choose from - stay with the attended feature or switch to a new feature - can be decoded in the frontopolar activation pattern (Güldener et al., 2019). **Expected results**: Using MVPA-methods (Hanke et al., 2009) we will investigate if not only switch-related activation but also feature represent-tation originates from supragranular layers, as suggested by the neural architecture. We expect WP1.3 to proceed in the last year of the funding period with a sample of n=25 young participants with support from Z02. By then, results from WP2.3, which will analyse layer-specific neuronal activity in the gerbil, will directly guide further hypotheses for this WP.

Work package 2 (animal studies):
WP2.1 Probabilistic foraging task to investigate exploration/exploitation behaviour.
In WP 2, we adapt a probabilistic foraging task (Lottem et al., 2018) in which gerbils can exploit a given foraging site to receive food by nose poke behaviour (Homma et al., 2016; 2017). They receive a food pellet with a random probability schedule that decays exponentially per foraging attempt to zero. In contrast to a deterministic task, rule change cannot be inferred from a single reward omission, but is based on accumulating, gradual evidence. The stochastic nature of action-outcome associations inevitably leads animals to sample both sides (Karlsson et al., 2012). Gerbils infer from the statistics of food delivery when to leave a ‘depleted site’ and explore another site to the costs of traveling and uncertainty of future food reward at another food source (Hayden et al., 2012)—in close correlation to the human foraging paradigm in which subjects also choose voluntarily to switch visual search patches. Through controlled and partial access to food, gerbils will be held to 85 % of their body weight, which guarantees sufficient motivation to forage food (average daily food ratio: 8 g). With pellets of 20 mg supplied during the task, we assume to be able to record nearly 200-300 ‘foraging attempts’ per day. During foraging, animals will be placed in an elongated chamber (100x25 cm) with ‘foraging spouts’ at each end and transposed walls as obstacles in between (cf. Fig. 4A). We will use the decay of reward probability and alternative costs (travel distance by obstacles) in order to shape exploratory vs. exploitative attentional resource strategy shifts of the foraging behaviour (Hayden et al., 2012). By video tracking, visits close to the spouts (region of interest; ROI) will be counted as ‘foraging trial’ as the period from entry until the exit of the ROI. With each entry into one of the ROIs, reward probabilities will be set to 1 and decline exponentially with each poke. A re-entry into the same ROI after leaving will be unrewarded and counted as ‘error trial’ (cf. Lottem et al., 2019). We assume that no time-consuming training is necessary, as animals quickly gain interest in the nose poke spout once they recognised that it will deliver food (Homma et al., 2016, 2017).

In this first part, we compare two groups of normal-aged (3 month) and elderly (two years) gerbils (each n=10) in this task (Cheal, 1986). Acquiring data over 3-4 weeks will enable us to optimise task parameters and probabilistic reward regimes (cf. Lottem et al., 2018). We assume to find an age-related change of attentional resource allocation in the old animals showing more pronounced exploitation behaviour motivated by findings in the human part of WP1.3 (cf. Düzel et al., 2010). Lastly, **we will test if voluntary wheel running over five weeks in the homecage may compensate for potential deficits in exploratory resource allocation in animals from the older cohort** (Morgan et al., 2018), in congruency to the human training interventions in WP 1.3 (n=10). **Expected results:** We here test our hypothesis that **older gerbils tend to spend longer times at their current sites compared to their normal aged littermates**, whose patch leaving behaviour should more accurately follow the marginal value theorem (Chin et al., 2015) and **evaluate physical exercise as potential compensatory resource** in the elderly.

WP2.2 Exploration of unpredictably changing environments. In the first part, we examine exploration in a predictably changing environment. We will modify the foraging paradigm established in WP 2.1 to investigate the gerbil's ability to explore its environment in response to unpredictable changes of the environment in congruency to the human WP1.2 (cf. Constantino and Daw, 2015). When the gerbil starts to poke a spout, it will be rewarded with constant reward probabilities (p=0.80/0.90/0.95). After a variable number of nose pokes, the reward probability will be reduced to p=0.20/0.10/0.05, respectively. We will count the number of nose pokes after reward probability reduction as an indicator of the detrimental perseveration of exploitative behaviour. We assume that trade-offs between exploitation and exploration will show a sharper boundary, which will help to later on regress frontal cortex activity to either the actual processing of the alternative options or the representation of exploratory vs. exploitative action (cf. WP1.2). **Expected results:** According to our **hypothesis of a stronger bias to stick with the exploitation with age, behavioural boundaries for allocation to exploration may differ between normal and older littermates**, which we will test in this experiment (n=10 each).

WP2.3 Layer-dependent recordings from frontopolar micro-circuit activity. In this part, we will chronically record with laminar multielectrodes (Neuronexus) from the anterior frontal field A of gerbils (FrA: bregma 5.00, lambda 9.45; Radtke-Schuller et al., 2016), the region analogue to the human frontopolar cortex, while gerbils perform the probabilistic foraging task (n=10). Translaminar processing principles in the frontal cortex share certain common principles with the canonical cortical activation patterns (Douglas and Martin, 2007; Godlove et al., 2014). Laminar CSD recordings will allow us to investigate the underlying local layer-specific FrA micro-circuit activity during the foraging behaviour (Figs. 2A and 4A). Thereby, we will disambiguate if the allocation of exploitation or exploration strategies differentially orchestrates the FrA circuitry in a layer-dependent manner (Fig. 1, right). Consistently with our hypothesis derived in WP1.4, we suggest that **explorative behaviour correlates with increased frontal theta activity and cross-columnar activity spread in supragranular layers of frontal cortex** (cf. Cavanagh et al., 2012). In contrast, persistent working memory content is updated via recurrent corticoefferent feedback loops originating in infragranular layers (Avery and Kirchmar, 2015, 2017) in the potential service of the maintenance of exploitation strategies. We henceforth hypothesize that **change of a 'foraging site' will be correlated with stronger recruitment of upper layers, while deeper layer activity will coincide with the exploitation of a given foraging site** (Fig. 1, right). *In vivo* data obtained from the frontal cortex in the gerbil will directly inform layer-specific fMRI experiments in humans (WP 1.4) Further, high gamma oscillations have a regulatory function for the strategy switch (Quilodran et al., 2008; Karlsson et al., 2012) which motivates us to analyse time-frequency changes and cross-laminar coupling (Deliano et al., 2018) as potential neural resource of explorative behaviour.

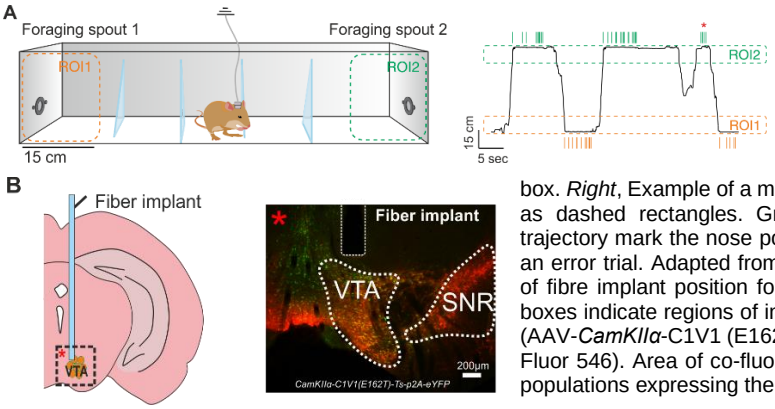


Fig. 4. Probabilistic foraging task and intervention with dopaminergic neurotransmission. A. *Left*, Schematic illustration of the foraging task in which gerbils can access food by shuttling back and forth between two 'Foraging spouts' 1 and 2 located at the opposite ends of the elongated box. *Right*, Example of a movement trajectory between both ROIs marked as dashed rectangles. Green or orange ticks above and below the trajectory mark the nose poke (foraging attempt). The red asterisk marks an error trial. Adapted from Lottem et al., (2018). B. Schematic overview of fibre implant position for optogenetic stimulation of the VTA. Dashed boxes indicate regions of interest shown in large: co-fluorescence of YFP (AAV-*CamKIIα*-C1V1 (E162T)-p2A-eYFP) and TH-immunostaining (Alexa Fluor 546). Area of co-fluorescence is indicative of overlapping neuronal populations expressing the virus and TH mainly found in the VTA.

Specifically, we can critically test the hypothesis of **layer-specific high gamma oscillations as processing capacity for reward coding during exploitation and error coding during exploration, respectively** (Rothé et al., 2011; Quilodran et al., 2008; Karlsson et al., 2012).
In order to calculate relative value estimates that might instrumentally guide the behavioural strategy at hand, we will use a Q-learning algorithm based on a delta rule (Klein et al., 2017). We suppose we will find value estimates to be present during phases of exploitation - as found in our recent preliminary work (cf. Fig. 3). We conjecture that **relative value correlates would incrementally diminish before the subject would start to explore the other foraging site**. Furthermore, the continuous build-up of evidence before the switch to exploration, as for instance modelled by random walk models (Gold & Shadlen, 2007), will be tested on CSD data with complementary deconvolution analysis methods adapted from the human part in WP1.1. **Expected results:** In this part, we aim to describe layer-specific correlates of frontopolar processing underlying attentional resource allocation in the gerbil.

WP2.4 Dopamine dependence of the trade-off between exploitation and exploration strategies. The frontal cortex is strongly innervated by dopaminergic input from the VTA encoding success or uncertainty in the brain (Schultz, 2015). Frontal dopamine has further been related to the incentive choice, which means the tendency to differentially weight costs and benefits (Salamone et al., 2005). Dopamine might hence bias decisions toward options with larger uncertainty promoting exploration strategies (Dezza et al., 2017; Cinotti et al., 2018; Tobler et al., 2005).
We want to utilize the layer-dependent influence of neuromodulatory circuits on frontopolar processing. Optogenetic activation of the VTA, established in our laboratory (Brunk et al., 2019; Fig. 4B), is a suitable tool, as it has been demonstrated that tonic D1-mediated dopamine acts predominantly in supragranular layers, while infragranular layer networks are susceptible to phasic VTA dopamine input (Avery and Kirchmar, 2015; Happel, 2016). Optogenetic approaches will be used in collaboration with **B01**-Sauvage/Prigge. We hypothesize that **phasic and tonic VTA stimulation may shift activity in the frontopolar cortex towards pronounced upper layer and deeper layer recruitment, respectively, specifically shifting exploration/exploitation trade-offs** (Fig. 4D). In a first set of experiments, we will assess layer-specific effects of VTA stimulation on aPFC processing by *in vivo* recordings (n=10). Secondly, the same animals will be probed in the probabilistic foraging task. **Expected results:** By applying trial-by-trial phasic or tonic VTA activation we will test if different firing modes potentially promote explorative or exploitative attentional resource strategies, respectively.

3.4.3 Timetable

	2020		2021				2022				2023				2024	
	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
WP 1-1																
WP 1-2																
WP 1-3																
WP 1-4																
WP 2.1																
WP.2.2																
WP2.3																
WP2.4																

3.4.4 Long-term perspective

The first funding period is meant to lay the foundation for a mechanistic understanding of exploration processes on the level of the meso- and micro-scopic neural architecture. Beyond this, we would like to investigate the following issues:

- If exploratory resource allocation is a prerequisite for successful transfer of learning, can we modulate transfer by biasing the exploration/exploitation balance?
- How does aPFC interact with the temporal lobe (particularly human MTL (Benoit et al., 2011; Gluth et al., 2015))? How is exploratory attention biased by memory?
- In cooperation with **Z01**-Angenstein/Kreutz/Storck, we plan to use layer-dependent high-resolution fMRI and CaMPARI2 technique in order to image active neural engrams and networks across the macro- and meso-scale in the gerbil frontopolar cortex during exploration-exploitation trade-offs.
- Can we compensate for deficits by guided plasticity of the neural architecture induced by training (guided by results from WP1.3 and WP2.1 in 1st period)?

- What are the limits in adaptation to environmental changes that the gerbil can achieve to secure an optimal adaptation/exploitation balance? What is the specific role of human frontopolar cortex in this context that cannot be achieved by the gerbil?
- APFC is directly connected only to other supramodal areas. However, how does aPFC, together with the other network areas like IFJ and MTL change attentional modulation in primarily visual and auditory cortices (Wang et al., 2019)?

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