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SUMMARY

The human brain undergoes remarkable changes over the lifespan, including its structural as well as functional characteristics. One functional change that has been identified in the brain of older adults is the phenomenon of *neural dedifferentiation*. This describes a process in which neural responses lose specificity over the course of aging, rendering neural representations of, for instance, distinct visual categories increasingly similar to each other. Findings in non-human animals have shown that tuning profiles of neural populations over a continuous stimulus space (e.g. an object's rotation) become broader with age, effectively widening the spectrum of stimuli that a single neuron responds to. Although research in humans has drawn on this finding as a potential mechanism for age-related dedifferentiation, it has not yet tested whether this process occurs for neural representations of continuous space. This presents a disconnect between the work on neural dedifferentiation in humans on the one hand, and animal work on its mechanisms on the other. The main goal of this dissertation was to address this disconnect and to further understand how aging shapes representations of continuous spaces. To achieve this, the three research articles that form the main body of this dissertation focus on the cognitive domains of spatial navigation and reinforcement learning.

Article I analyzes functional magnetic resonance imaging (fMRI) data collected during virtual spatial navigation of older and younger adults and presents evidence that the phenomenon of age-related neural dedifferentiation in humans extends to representations of a continuous variable, namely walking direction. The results are based on a newly introduced analysis approach that allows the field to assess the similarity of neural responses towards stimuli stemming from the same continuous space.

Article II combines a double-blind cross-over drug intervention with a design similar to *article I* and investigates the mechanistic role of the transmitter dopamine in age-related neural dedifferentiation. The study replicates the findings of *article I* and confirms the causal role of neuromodulation on the specificity of neural representations suggested by computational models. In particular, results show that the administration of L-DOPA, a dopamine precursor, enhances the specificity with which different walking directions are represented in the brain of younger and older adults.

Finally, *article III* moves towards more abstract continuous space and uses a reinforcement learning paradigm to assess how a younger and older age group learn from surprising events. More specifically, it investigates if prediction errors, a continuous quantity reflecting the difference between an expected and obtained outcome of an action, are represented differently in learning and behavior of younger and older individuals. Behavioral results indicate that older adults showed heightened sensitivity to surprise compared to younger adults, overrepresenting the extreme end of the continuous space of prediction errors in their decisions.

In summary, this thesis has made a number of contributions towards our understanding of how aging influences representations of continuous space. For one, it provides the first evidence of age-related neural dedifferentiation of a continuous variable in humans, based on a newly developed analysis approach. In doing so, it closes an important gap between related research in humans and non-human animals. It furthermore accounts for a key mechanism of dedifferentiation, confirming the causal influence of dopamine on the specificity of neural representations, as predicted by computational models. Finally, the thesis shows that diverging representations of continuous space in older adults also extend to the more abstract domain of outcome-based learning.

ZUSAMMENFASSUNG

Das menschliche Gehirn unterliegt im Laufe des Lebens bemerkenswerten Veränderungen, die sowohl strukturelle als auch funktionelle Eigenschaften betreffen. Eine funktionelle Veränderung, die insbesondere im Gehirn älteren Erwachsenen festgestellt wurde, ist das Phänomen der neuronalen Dedifferenzierung. Dies beschreibt einen Prozess, bei dem die nervlichen Reaktionen im Laufe des Alterns an Spezifität verlieren, so dass die neuronalen Repräsentationen z.B. verschiedener visueller Kategorien einander immer ähnlicher werden. Untersuchungen an Tieren haben gezeigt, dass die Reaktionsprofile neuronaler Populationen über einen kontinuierlichen Reizraum (z.B. die Drehung eines Objekts) mit zunehmendem Alter breiter werden, wodurch sich das Spektrum der Reize, auf die ein einzelnes Neuron reagiert, effektiv erweitert. Obwohl die Forschung am Menschen auf diesen Befund als einen der möglichen zugrundeliegenden Mechanismen hingewiesen hat, konnte eine altersbedingte Dedifferenzierung bisher nicht für neuronale Repräsentationen eines kontinuierlichen Raums nachgewiesen werden. Dies stellt eine Diskrepanz zwischen den Arbeiten zur neuronalen Dedifferenzierung beim Menschen einerseits und den Arbeiten zu den zugehörigen Mechanismen bei Tieren andererseits dar. Das Hauptziel dieser Dissertation war es, diese Diskrepanz zu beseitigen und besser zu verstehen, wie das Altern die Repräsentation von kontinuierlichen Räumen formt. Um dies zu erreichen, konzentrieren sich die drei Forschungsartikel, die den Hauptteil dieser Dissertation bilden, auf die kognitiven Bereiche der räumlichen Navigation und des Verstärkungslernens.

In *Artikel I* analysiere ich Daten der funktionellen Magnetresonanztomographie (fMRI), die während der virtuellen räumlichen Navigation älterer und jüngerer Erwachsener erhoben wurden. Ich präsentiere Belege dafür, dass das Phänomen der altersbedingten neuronalen Dedifferenzierung beim Menschen auch Repräsentation einer kontinuierlichen Variable, nämlich der Laufrichtung, betrifft. Die Ergebnisse basieren auf einem neu eingeführten Analyseansatz, der es erlaubt, die Ähnlichkeit der neuronalen Reaktionen auf Reize zu bewerten, die aus demselben kontinuierlichen Raum stammen.

Artikel II kombiniert eine doppelblinde Cross-over-Medikamentenintervention mit einem ähnlichen Design wie *Artikel I* und untersucht die mechanistische Rolle des Transmitters Dopamin bei altersbedingter neuronaler Dedifferenzierung. Die Studie repliziert die Ergebnisse von *Artikel I* und bestätigt die kausale Rolle der Neuromodulation auf die Spezifität der neuronalen Repräsentationen, wie sie von Computermodellen vorhergesagt wurde. Insbesondere zeigen die Ergebnisse, dass die Verabreichung von L-DOPA, einer Dopaminvorstufe, die Spezifität mit der verschiedene Laufrichtungen im Gehirn von jüngeren und älteren Erwachsenen repräsentiert werden erhöht.

Artikel III schließlich befasst sich mit einem abstrakteren kontinuierlichen Raum und verwendet ein Paradigma des Verstärkungslernens, um zu untersuchen, wie sich jüngere und ältere Menschen beim Lernen von überraschenden Ereignissen unterscheiden. Genauer gesagt wird untersucht, ob Vorhersagefehler, eine kontinuierliche Größe, die die Differenz zwischen der erwarteten und der erhaltenen Belohnung einer Handlung widerspiegelt, im Lernen und Verhalten von jüngeren und älteren Personen unterschiedlichen Einfluss nehmen. Die Ergebnisse zeigen, dass ältere Erwachsene im Vergleich zu jüngeren Erwachsenen eine erhöhte Empfindlichkeit gegenüber überraschenden Belohnungen zeigen und, dass das extreme Ende des Kontinuums der Vorhersagefehler in ihren Entscheidungen größeren Einfluss nimmt.

Zusammenfassend lässt sich sagen, dass diese Arbeit eine Reihe von Beiträgen zu unserem Verständnis darüber geleistet hat, wie das Altern die Repräsentationen des kontinuierlichen Raums beeinflusst. Zum einen liefert sie auf der Grundlage eines neu entwickelten Analyseansatzes den ersten Nachweis für altersbedingte neuronale Dedifferenzierung im Kontext einer kontinuierlichen Variable. Damit schließt sie eine wichtige Lücke zwischen verwandten Arbeiten in Menschen und nicht-menschlichen Tieren. Bezüglich der Mechanismen der neuronalen Dedifferenzierung bestätigt sie darüber hinaus den kausalen Einfluss von Dopamin auf die Spezifität neuronaler Repräsentationen, wie von Computermodellen vorhergesagt. Schließlich zeigt die Arbeit, dass divergierende Repräsentationen des kontinuierlichen Raums bei älteren Erwachsenen auch im abstrakteren Bereich des ergebnisbasierten Lernens präsent sind.

ACRONYMS

AD Alzheimer's disease.

BOLD blood-oxygen-level-dependent.

DA dopamine.

EEG electroencephalography.

EVC early visual cortex.

fMRI functional magnetic resonance imaging.

GABA γ-Aminobutyric acid.

GLM general linear model.

HAROLD hemispheric asymmetry reduction in older adults.

HD head direction.

HRF hemodynamic response function.

L-DOPA Levodopa.

LR learning rate.

MCI mild cognitive impairment.

MTL medial temporal lobe.

MVPA multi-voxel pattern analysis.

ND neural dedifferentiation.

PASA posterior to anterior shift in aging.

PE prediction error.

PET positron emission tomography.

PFC prefrontal cortex.

RL reinforcement learning.

ROI region of interest.

RSC retrosplenial cortex.

STAC scaffolding theory of aging and cognition.

VR virtual reality.

LIST OF ORIGINAL RESEARCH ARTICLES

This doctoral thesis is based on the following three original research articles:

Article I

Koch, C., Li, S.-C., Polk, T.A., & Schuck, N.W. (2020). Effects of aging on encoding of walking direction in the human brain. *Neuropsychologia*, *141*, 107379. doi: 10.1016/j.neuropsychologia.2020.107379

Article II

Koch, C., Baeuchl, C., Glöckner, F., Riedel, P., Petzold, J., Smolka, M.N., Li, S.-C., & Schuck, N.W. (2022). L-DOPA enhances neural direction signals in younger and older adults. *NeuroImage*, *264*, 119670. doi: 10.1016/j.neuroimage.2022.119670

Article III

Koch, C., Zika, O., & Schuck, N.W. (2022). Influence of surprise on reinforcement learning in younger and older adults. *PsyArXiv*. doi: 10.31234/osf.io/unx5y

1

BACKGROUND

1.1 General Introduction

The aging brain does not have a good reputation. When we think about our cognitive abilities, especially those that allow us to quickly process or remember important information, many of us would not expect them to improve in older age. Maybe even quite the opposite. Often we tend to perceive the later stages of our life course as a period of consistent decline and deterioration. Just like we expect stereotypical changes in our sense of hearing and vision, we expect to take longer when performing mental operations or to more often forget about important information. But is this bad reputation deserved? Is downwards really the only direction the aging brain is heading? Questions such as this lie at the core of the research field of lifespan development (Baltes & Lindenberger, 1997; Smith & Baltes, 1999; Baltes, Lindenberger, & Staudinger, 2007). As suggested by its name, lifespan development is concerned with how humans and other animals change over the entirety of the life course, including the youngest and oldest ages. The approach to aging taken in this field separate it from other, more naïve perspectives of aging. One defining difference and diverging from the viewpoint of mono-directional decline is that lifespan development considers the life course to be a dynamic interaction between losses and gains, even in the later stages of life (Baltes, 1987). From this perspective, loss is not the defining feature of older age. Rather, loss is encountered and reacted to, possibly with growth in other domains as the individual combines selective and compensatory behavior.

This thesis combines the perspectives of lifespan development with cognitive neuroscience and aims to contribute to a more thorough understanding of the human brain and behavior in older age. The aging brain has been the focus of a multitude of scientific work, identifying and describing age-related[1] changes in terms of structural as well as functional characteristics and relating them to older adults' developmental trajectories (see Riddle & Taylor, 2020

[1]To avoid confusion, I want to underline that the term *age-related* is used more loosely in this thesis to describe findings that considered age as an influential factor. If not specified otherwise, it does not imply, for instance, a linear relationship with years of age or within-person change assessed by longitudinal measurement. See Salthouse (2019) for further detail on the importance of being aware of this distinction.

and Samanez-Larkin, 2019, respectively). The individual articles forming the basis of this cumulative dissertation have been focused on age differences in the functional aspects. More precisely, they have gravitated around a particular functional phenomenon termed *neural dedifferentiation (ND)*. Age-related neural dedifferentiation is defined as the finding that older age is accompanied by reduced distinctiveness of neural representations[2] of perceptual and conceptual information (Koen & Rugg, 2019). Its presence has been suggested to play a role in cognitive decline (Li & Lindenberger, 1999), particularly in memory aging (Li & Freund, 2005). The projects included in this thesis are concerned with the age-related changes in neural representations, addressing open questions, and introducing new approaches in their investigation. The first project used functional magnetic resonance imaging (fMRI) to study the neural representations of direction during spatial navigation in older and younger adults (see *article I*). The second project used a drug-intervention to assess a related mechanism of change, particularly levels of the neurotransmitter dopamine (see *article II*). The third project used behavioral and computational modelling analyses to investigate representations of key variables in processes of outcome-based learning, including prediction errors and learning rates (see *article III*). However, before we consider the individual contributions in more detail it is important to do justice to the extensive amount of preceding research that allows for the existence of this thesis. The following section will therefore focus on what we know about the aging process and its remarkable variability, specifically in the context of the human brain and memory.

1.2 Variability in Aging

One of the most significant changes humans encounter in the later stages of the life course regards memory function. A loss in memory performance is part of a normative aging process and not exclusive to pathology (Tucker-Drob, 2019). As an essential part of our everyday life, age-related changes in our ability to remember are a target of personal worry (Kessler, Bowen, Baer, Froelich, & Wahl, 2012) and adapting to them presents a key challenge of older age. What

[2]The term *neural representation* is used throughout this thesis to describe a measurable neural response elicited by, and containing information about, a specific component of the outside world. In humans this is usually assessed by techniques of non-invasive neuroimaging such as functional magnetic resonance imaging. For more detail on the notion see Dietrich (2007) and Vilarroya (2017).

quickly becomes evident when looking at the change of memory function with age is that it is more complex than what the brain's "bad reputation" for continual decline (see above) might suggest. Extensive research of the trajectories of memory function over the life course has shown that the effects of age differ strongly depending on the domain in question (Brickman & Stern, 2009; Nyberg, Lövdén, Riklund, Lindenberger, & Bäckman, 2012) and the type of measurement used (longitudinal vs. cross-sectional, Baltes & Schaie, 1974; Hofer & Sliwinski, 2001). To illustrate, cross-sectional approaches to study the domains of *episodic* memory and *working* memory have reported linear drops in performance as early as the third decade of life (Nilsson et al., 1997; Verhaeghen & Salthouse, 1997). In contrast, *semantic* and *procedural* memory were found to follow a more positive age gradient, showing an increase in performance up to a much higher age (D. C. Park et al., 2002; Nyberg et al., 2012; Nyberg & Pudas, 2019). But when we look at longitudinal studies, more resistant to potential confounds such as cohort effects, they have reported stable episodic memory performance up into the seventh decade of life (Schaie, 1994; Schaie, Willis, & Pennak, 2005; Rönnlund, Nyberg, Bäckman, & Nilsson, 2005) followed by a more rapid deterioration (Gorbach et al., 2017). Proxy measures provide evidence that similar changes might also apply in the domain of working memory (Rönnlund & Nilsson, 2006). Approaches that measure the same individual over multiple time points therefore show us that the idea of an early and consistently declining brain might not be an accurate depiction.

One of the reasons for these strong differences between cross-sectional and longitudinal approaches, which is often overlooked in the results on the population level, is that the inter-individual variance of aging trajectories is vast (Wilson et al., 2002; Lindenberger & Ghisletta, 2009; Lindenberger, 2014). Acknowledging these substantial differences between individuals requires a more thorough differentiation when describing aging trajectories of cognitive abilities. The spectrum of possible paths reaches from pathological aging in the face of disease to the so-called *successful* aging (see Rowe & Kahn, 1987, 2015), where cognitive functioning is maintained until very old age (Depp & Jeste, 2006). One of the central goals of the corresponding scientific literature is to understand how some, but not all, older adults are capable of this maintenance, even in the presence of brain pathology (see Nyberg & Pudas, 2019).

Over the years, several concepts have been proposed to capture this resilience against aging or disease. From a cognitive neuroscience standpoint, the human brain plays an important role

in these concepts. Both the brain's structural as well as its functional properties have been credited in the making of differential trajectories of aging. Regarding mainly the structural aspects of the human brain, Nyberg et al. (2012) introduced the concept of *brain maintenance* as one primary characteristic of successful memory aging. Individuals that show high brain maintenance would be best described by an absence of pathology and by a minimization of the age-related changes that brain tissue is subject to. Healthy humans over 65 years of age experience a decrease in whole brain volume averaging to 0.45% per year (Fotenos, Snyder, Girton, Morris, & Buckner, 2005). Studies have further shown that less age-related changes in global tissue integrity (i.e. brain maintenance) were associated with less decline of global cognitive functioning (Fletcher et al., 2018; Cox et al., 2021). Such change-change relationships between structural integrity and cognitive decline have also been investigated in the more specific context of episodic memory. Results showed that volume changes in older adults, particularly in the medial temporal lobe (MTL), are related to are related to changing episodic memory performance (Johansson et al., 2022). When looking at the structural aspects, evidence therefore seems to support the idea that maintaining the brain's morphologic integrity might be one major hallmark in the determination of cognitive aging trajectories. How this process can potentially be supported is still subject to extensive research. However, promising findings have been presented with regard to (epi-)genetics, education, and physical activity (for a review, see Nyberg & Pudas, 2019).

The maintenance of the brain's structural integrity is not the only aspect that might support a healthy aging processes. Instead of being able to resist or avoid pathology (brain maintenance), successful aging might depend on *neural reserve*, the ability of the brain to *cope* with pathology (Alvares Pereira, Silva Nunes, Alzola, & Contador, 2022; Stern et al., 2020). While structural properties of the brain also play a major role by providing the "neurobiological capital" (Stern et al., 2020, p. 1308) to cope with age-related brain changes (like in brain maintenance), the idea of reserve also goes beyond the passive concept of available resources. What has been termed *cognitive reserve*, a theoretical concept defined by Stern (2002), is a more active process in which the individual can cope with pathology by altering functional properties of the brain. It is defined as "the adaptability (...) of cognitive processes that helps to explain differential susceptibility of cognitive abilities (...) to brain aging, pathology, or insult" (Stern et al., 2020, p. 1306). This adaptability might be expressed in, for instance, the

recruitment of alternative brain networks to solve the same task in case senescent brain change made other solutions unavailable.

The notion of functional adaptability is inconsistent with the aging brain's "bad reputation" as a supposed subject of consistent and inevitable decline. It illustrates that the brain of older adults is not to be perceived as a static system, but that it is embedded in an ongoing process of development. The topic of functional changes in the aging brain is central to this dissertation. In the following section I will specifically focus on the literature of functional changes in the aging brain and how they benefit cognition in the face of neural compromise. Keeping in mind the concept of cognitive reserve, I will first introduce the hallmarks of *compensatory* age-related functional brain changes. We will afterwards talk about their limitations and present a different notion towards functional changes in the aging brain, those that are not directly linked to beneficial consequences for cognition. This will lead us toward one particular functional difference between the brains of older and younger adults central to this dissertation: the phenomenon of neural dedifferentiation (ND).

1.3 Changes in Memory-Related Brain Signals with Age

What researchers mean when speaking of so-called *functional* measurements are recordings of the brain's activity over a period of time, often while participants are solving cognitive tasks. Obtaining these measures can be achieved via functional neuroimaging techniques including, for instance, fMRI and positron emission tomography (PET), with either offering different perspectives and advantages. Such measurements offer a more elaborate look into the process of aging, going beyond the investigation of changes in the brain's structural integrity. They allow researchers to investigate what influence age has on the inner workings of cognition and how younger and older adults might differ in the way they utilize the resources offered by their respective brains. For example, we learned that reaching older age is accompanied by tissue loss in the MTL, which was specifically linked to age-related changes in memory performance (Johansson et al., 2022). Focusing on the functional changes in the aging brain in this case helps us to understand how, in the face of such structural compromise, the cognitive processes involved in memory are affected

A study by Gutchess et al. (2005) investigated the link between brain activity during en-

coding and recall of episodic memory content in younger and older adults. One central result was that MTL activity was generally weaker during the encoding process in older compared to younger adults, which they interpreted to be in line with the age-related loss of tissue reported in previous research (see Raz, 2000). However, this finding went hand in hand with a pattern that considerably shaped many following models of brain aging: the relatively weaker recruitment of the MTL during encoding in older adults was accompanied by *increased* prefrontal activation, an *overactivation* compared to younger adults. This finding speaks in favor of the idea that memory deficits in older age might not be characterized by overall decreasing brain signals but rather by more complex functional changes, with strong support coming from other neuroimaging studies. Works utilizing PET were among the first to report this pattern in older adults (Bäckman et al., 1997; Grady et al., 1992) but have since then been joined by a number of fMRI studies and comprehensive meta-analyses (Spreng, Wojtowicz, & Grady, 2010; Spreng, Shoemaker, & Turner, 2017; G. R. Turner & Spreng, 2012). When compared to younger adults across several cognitive domains, including memory encoding and retrieval, older individuals exhibited stronger recruitment of specifically the prefrontal cortex (PFC) across all investigated domains (Spreng et al., 2010; Spreng & Turner, 2019). Therefore, the overactivation of the PFC is now a fairly established phenomenon found in the aging brain. Regarding the consequences of this overactivation, Gutchess et al. (2005) also reported that it was correlated with *increased* memory performance in the older age group. Such links between overactivation and increased performance have also been made in domains other than memory encoding, such as memory recall (Cabeza, Anderson, Locantore, & McIntosh, 2002) or motoric coordination (Heuninckx, Wenderoth, & Swinnen, 2008). This suggests that such elevated fMRI signals in older adults might reflect additional recruitment of neural resources for the purpose of maintaining a "younger" level of performance, effectively taking a *compensatory* function (Reuter-Lorenz & Lustig, 2005; Reuter-Lorenz & Cappell, 2008). When we touched upon the theoretical concept of cognitive reserve in the previous section in order to introduce the idea of functional brain changes, the compensatory recruitment of PFC networks is a prime example of the functional adaptability Stern et al. (2020) referred to. This functional compensation is not necessarily a result of intent, opposed to, for instance, forms of actively pursued behavioral compensation (Baltes & Baltes, 1990) like writing down important dates in order to remember

them. Yet, overactivation has been linked to positive effects on performance[3] in a variety of studies, including healthy (Vallesi, McIntosh, & Stuss, 2011; Du, Buchsbaum, Grady, & Alain, 2016; Gallen, Turner, Adnan, & D'Esposito, 2016) and clinical samples (Lenzi et al., 2011; Meltzer, Wagage, Ryder, Solomon, & Braun, 2013; Elman et al., 2014), as well as a number of different cognitive domains (Berlingeri et al., 2010).

Multiple theoretical accounts have been made to explain findings that suggest compensatory functional changes in the aging brain (for reviews, see Spreng & Turner, 2019; Zahodne & Reuter-Lorenz, 2019; Reuter-Lorenz & Cappell, 2008). Some of them have been focused on specific findings such as the *posterior to anterior shift in aging* (PASA; S. W. Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008) hypothesis, proposing that weaker activation in posterior parts of the brain like the MTL is answered by compensatory activation in frontal regions, or the *hemispheric asymmetry reduction in older adults* (HAROLD; Cabeza, 2002) describing beneficial effects of older adults recruiting bilateral brain areas shown across multiple domains (Cabeza, 2004). One model that tries to embed these in a larger conceptualization of brain aging is the *scaffolding theory of aging and cognition* (STAC/STAC-r; D. C. Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Park, 2014). *Scaffolding* here describes the process through which the brain forages new neural circuits ("scaffolds") in response to challenges arising from older age, in order to maintain its level of cognitive functioning. These compensatory scaffolds offer a replacement to other, more efficient circuits that are affected by age-related changes including the previously mentioned anatomical deterioration in grey- but also in white matter (Raz et al., 2005; Wen & Sachdev, 2004; Bennett & Madden, 2014) as well as functional changes, such as decreased MTL activity (Gutchess et al., 2005). The STAC is a powerful framework in the sense that it can account for specific findings, like the recruitment of homologous brain areas (see Cabeza, 2002), by including the respective regions in the new scaffolds. At the same time it offers a more general account for the phenomenon of overactivation, considering additional factors such as structural change or experiences made over the life course (for a comprehensive review on those factors, see Reuter-Lorenz & Park, 2014). However, what especially sets it apart from other models is its more elaborate account towards the limitations and costs of using

[3]Note that compensatory effects are investigated within-group, e.g. by assessing if cognitive deficits in the older age group are less severe in the presence of overactivation. Compensation does not require equal or even better performance than the reference group.

overactivation for compensatory processing. For instance, task demand has been credited as a limiting factor for the compensatory effect of overactivation (Reuter-Lorenz & Lustig, 2005). Due to compensatory overactivation, older adults are thought to reach their neural resource ceiling earlier, ultimately leading to worse performance and decreased activation as task demands increase. Additionally, STAC proposes that newly emerging scaffolds in older age come with a cost for efficiency. While new scaffolds help to cope with other age-related changes, their usage requires more effort for the same result. Both of these, limitations (Cappell, Gmeindl, & Reuter-Lorenz, 2010; McEvoy, Pellouchoud, Smith, & Gevins, 2001; Diaz, Rizio, & Zhuang, 2016) as well as costs (Zarahn, Rakitin, Abela, Flynn, & Stern, 2007; Meunier, Stamatakis, & Tyler, 2014) of compensatory scaffolds have been supported by evidence stemming from neuroimaging studies.

So far, although there are associated limits and costs, we have seen that functional change in the aging brain can allow individuals to compensate for compromised neural structures and information processing to maintain performance (for a detailed review the reader is referred to Zahodne & Reuter-Lorenz, 2019). However, not all age-related changes in brain functioning have been explicitly linked to positive consequences for cognition. What has been hypothesized to be of particular importance in the process of cognitive aging is a decline in the brain's capacity to modulate neural signals (Gazzaley & D'esposito, 2007; Spreng & Turner, 2019). This line of research has shown that older age is associated with decreased specificity of neural representations, for example, in regions of the brain that usually exhibit category-specific activation profiles (e.g. the fusiform face area Payer et al., 2006; Gazzaley, Cooney, Rissman, & D'Esposito, 2005). This loss in neural distinctiveness has been termed *age-related neural dedifferentiation*. In contrast to the previously described changes, the role of neural dedifferentiation in aging is not thought to be compensatory. Instead, it is seen as a contributing factor in the decline of cognitive functioning (Li & Lindenberger, 1999; Li, Lindenberger, & Frensch, 2000). Age-related neural dedifferentiation takes a major role in this thesis' endeavor to understand how aging shapes neural representations. The next section will take a closer look into the phenomenon, the part it plays in cognitive aging, and the potential factors involved in its emergence. Finally, we will move towards open questions and lay the foundation for the individual works included in this thesis.

1.4 Neural dedifferentiation

To avoid confusion there is the need to specify what I mean when using the term age-related neural dedifferentiation (ND). Some have referred to ND as a domain-general pattern of functional change in aging (D. C. Park, Polk, Mikels, Taylor, & Marshuetz, 2001), describing "increased and more spatially distributed neural activity" (Spreng & Turner, 2019, p. 21) or that activity in the aging brain tends to be more disorganized in general (Craik & Bialystok, 2006). I will use the term in a more outlined manner, particularly referring to age-related decline in specialized neural mechanisms or their recruitment (Cabeza et al., 2002; Li, Lindenberger, & Sikström, 2001) so that older adults display less specific patterns of activation in response to certain content. This is illustrated best by a seminal study conducted by D. C. Park et al. (2004): in an fMRI experiment with older and younger participants they presented a number of visual stimuli stemming from different categories, including faces and scenes. After functionally defining sets of voxels in the ventral visual cortex that most strongly responded to each category, the authors compared both age groups on how voxel sets were activated in response to stimuli from each category. They showed that older adults exhibited less specific responses given by the fact that, for instance, faces resulted in higher activation of scene voxels in comparison to younger adults. This presented evidence for the deterioration of specialized information processing and less distinct neural signals in older age, i.e. age-related ND. In the following, I will elaborate on the current state of knowledge regarding age-related ND.

Neural dedifferentiation is a robust finding in fMRI studies

The idea that processes in the aging brain dedifferentiate originally stems from behavioral findings and intelligence research (Reinert, 1970; Lindenberger & Baltes, 1997; Baltes & Lindenberger, 1997). These findings suggested that performance across different cognitive and sensory tasks becomes more correlated as a person reaches older ages, showing less differentiated profiles of cognitive ability. While recent evidence suggests that it is not the cognitive abilities but rather their rate of change that dedifferentiates with age (de Frias, Lövdén, Lindenberger, & Nilsson, 2007; Tucker-Drob, Brandmaier, & Lindenberger, 2019), the potential neural correlates of dedifferentiation inspired a large body of subsequent work. As of today, ND has become a robust phenomenon reported in numerous fMRI studies (Koen & Rugg,

2019). Visual categories, as those used by D. C. Park et al. (2004), present the most commonly investigated domain in the context of ND. The age-related decrease of specificity in the neural responses elicited by different visual categories has been shown in a number of studies, with the most compelling evidence stemming from paradigms including faces and scenes, often houses (Zheng et al., 2018; Trelle, Henson, & Simons, 2019; Goh, Suzuki, & Park, 2010; Bowman, Chamberlain, & Dennis, 2019; Voss et al., 2008; Koen, Hauck, & Rugg, 2019; Carp, Park, Polk, & Park, 2011). But similar losses in specificity of representations have been reported also for phonemes in auditory cortices (Du et al., 2016) and different movement patterns in motor cortices (Carp, Park, Hebrank, Park, & Polk, 2011). The (rather) recent advances in multivariate analyses methods in the field of neuroimaging have furthermore allowed a more fine grained perspective on the topic via multi-voxel pattern analysis (MVPA, Haxby et al., 2001) and multivariate classification (Carp, Park, Hebrank, et al., 2011; Carp, Gmeindl, & Reuter-Lorenz, 2010; Zheng et al., 2018; Koen, 2022; for a special issue on this, see Dennis & Koen, 2022). Carp, Park, Polk, and Park (2011) revisited the paradigm of D. C. Park et al. (2004) utilizing an MVPA approach. By assessing how similar patterns of voxels are that were evoked by the same visual category (e.g. faces) and how different they are to patterns evoked by another category (e.g. houses) the authors calculated a measure of *neural distinctiveness*. In line with previous findings, this distinctiveness was again lower in older adults in the ventral visual cortex, with further differences detected in early visual areas, the PFC, and the inferior parietal cortex.

Dedifferentiation is related to worse memory performance

I have mentioned before that age-related ND is thought to be related to the decline of cognitive abilities. This assumption is built on computational models of cognitive aging (Li et al., 2001; Li & Rieckmann, 2014) which have linked lower fidelity of neural representations to decreasing fluid abilities (e.g. working memory, Li & Sikström, 2002) and associative memory (Li, Naveh-Benjamin, & Lindenberger, 2005). Studies that investigated these relationships were able to present evidence that measures of neural specificity are indeed linked to measures of cognitive performance (for reviews, see Koen & Rugg, 2019 and Koen, Srokova, & Rugg, 2020). When looking at fluid abilities, measured by psychometric test batteries, studies showed a positive correlation with neural differentiation across different object categories (faces, houses, and

objects, Koen et al., 2019; D. Park, 2010). Those individuals with more specific representations of visual categories therefore tended to perform better on psychometric tests. Similar findings could be presented for episodic memory (St-Laurent, Abdi, Bondad, & Buchsbaum, 2014; St-Laurent & Buchsbaum, 2019; Zheng et al., 2018). Related to the idea that more distinct information present during encoding offers a mnemonic benefit (Murdock, 1960; R. R. Hunt, 1995), Koen et al. (2019) showed a positive relationship between the recognition of visual scenes and the specificity with which the parahippocampal place area could represent them. Such a benefit of neural specificity was also shown during memory retrieval (Bowman et al., 2019). Interestingly, in the majority of these studies this relationship was not moderated by the participant's age. This points into the direction that the link between ND and memory performance might be stable across the adult lifespan (Rugg, 2016) which conforms with the computational models that linked ND and cognitive decline in an age-invariant manner (Li & Rieckmann, 2014).

The ND of memory content present during encoding or retrieval is therefore likely among the neural factors involved in memory aging. If we want to better our understanding of the cognitive aging process, it will prove useful to expand our knowledge regarding age-related ND, which representations it affects, and the mechanisms involved in its emergence. Computational models that have already proven useful in predicting the mnemonic consequences of ND have also been explicitly linked to its potential mechanisms, the topic of our next section.

Age-related changes in neural tuning and transmitter systems are supposed mechanisms of neural dedifferentiation

Accounts of the mechanisms involved in age-related ND target small-scale processes that are hard to investigate with non-invasive methods of neuroimaging. For instance, mechanistic importance has been assigned to the neurotransmitter system or the firing patterns of individual neurons. In turn, much of the empirical work on the mechanistic background of ND has been conducted in animals. Although this research has identified multiple suspected mechanisms, it is important to note that they were not proposed as exclusive. It is more likely that they are happening in parallel and are, at least to some degree, interdependent.

Neuromodulation is a central concept in the model by Li et al. (2001) which was introduced in the section on cognitive consequences arising from reduced neural specificity. More

specifically, the model proposes that reductions in *neural gain* lead to more noisy output on the population level. Neural gain is a parameter describing how strongly a neuron's firing is controlled by afferent signals. This relationship is characterized by a logistic activation function. Simulations have shown that, while "younger" networks are able to activate separate sets of units for different tasks, "older" networks with reduced neural gain fail to do so. As a consequence, the distinct sets are activated in both tasks (Li et al., 2001; Li & Sikström, 2002). The model specifically mentions the neurotransmitter dopamine (DA) as its biological basis, a so-called *neuromodulator* that helps to elevate neural signals over the present background noise (Sawaguchi, Matsumura, & Kubota, 1988), similar to the model's gain parameter. What makes the model by Li et al. (2001) a plausible candidate in the explanation of ND is that research has shown DA receptors (D_1 as well as D_2) deplete with older age (Wong, Young, Wilson, Meltzer, & Gjedde, 1997; Y. K. Yang et al., 2003). Relatedly, evidence for the role of DA in age-related memory impairment has been stemming from multiple sources, including patients, cellular recordings, and computational modelling (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006). What is, however, still lacking is evidence for an effect of DA on the specificity of neural representations in humans. Investigating the influence of DA in the context of age-related ND will be one of the main objectives of this thesis.

Another account of the mechanisms of ND is based on findings provided by single-unit recordings in the brain of aging non-human animals. Schmolesky, Wang, Pu, and Leventhal (2000) showed rotating bars and gratings to young and old macaque monkeys and recorded the firing patterns of neurons in the striate cortex. They investigated age-related changes in particular cells in V1 that exhibit firing patterns tuned to a preferred orientation of visual stimuli (Hubel & Wiesel, 1968) where the number of elicited action potentials are a function of the encountered orientation. This tuning function is characterized by a Gaussian curve with a maximum firing rate at a preferred orientation (different for each neuron) and a stronger decrease in firing the more the encountered orientation diverges from this preference. In their study, Schmolesky et al. (2000) could show that selectivity (or "orientational bias") of these cells is weaker in older monkeys which was expressed in maximum firing rates for a broader window of orientations. They referred to this loss of tuning specificity as *neural broadening*, a widening of the neuron's receptive field resulting in increased response to non-preferred stimuli. Such wider receptive fields in the cells of senescent non-human animals could also be

identified in the domains of somatosensory (David-Jürgens, Churs, Berkefeld, Zepka, & Dinse, 2008; Spengler, Godde, & Dinse, 1995) and auditory processing (Kamal, Holman, & de Villers-Sidani, 2013; Costa, Lepore, Prévost, & Guillemot, 2016; J. G. Turner, Hughes, & Caspary, 2005) and also in more downstream visual areas responsible for processing the direction of an object's movement (MT; Y. Yang et al., 2008; Liang et al., 2010). Evidence for why aging might lead to these sort of changes was provided by Leventhal, Wang, Pu, Zhou, and Ma (2003). They found that the administration of a γ-Aminobutyric acid (GABA) agonist could restore specificity of tuned cells in older monkeys to the point at which patterns again resembled those of younger animals, strongly suggesting a role of diminished intracortical inhibition with age. While evidence for the importance of GABA is still sparse in humans, a recent study by Lalwani et al. (2019) combined fMRI with MR spectroscopy to investigate ND in the human auditory cortex while non-invasively measuring the concentration of GABA in different areas of the brain. They were able to show that an age-related dedifferentiation of auditory neural signals was negatively associated with levels of GABA in the auditory cortex, but not in other areas, suggesting that GABA might also play an important role in human ND.

In contrast to an increase of responses to non-preferred stimuli (neural broadening), what could also lead to less specific population-level signals is a loss in a neuron's preference all together. What is summarized under the term *neural attenuation* is that neurons fire less in response to previously preferred stimuli (J. Park et al., 2012), an idea that links to findings of fMRI underactivation in older age (Gutchess et al., 2005; Spreng et al., 2010). On the single-unit level, Schmolesky et al. (2000) ruled out neural attenuation as an explanation for their findings by showing that peak firing rates in older monkeys were not decreased. However, a large-scale fMRI study investigated the possible contributions of both mechanisms, broadening and attenuation, towards age-related ND on the population level by comparing representations of faces and houses in 310 participants (J. Park et al., 2012). They investigated if dedifferentiation was stemming from an increased response to non-preferred stimuli (neural broadening) or from decreased responses to preferred stimuli (neural attenuation). Interestingly, the study could present evidence for both processes depending on the investigated region, the fusiform face area or the extended face network (Ishai, 2008). This underlines what was mentioned before: the processes involved in ND are not mutually exclusive but might be happening in parallel.

Investigating neural dedifferentiation over a continuous space will close an important gap between animal and human work

When we think about the potential single-cell mechanisms (broadening or attenuation) on the one hand and the population-level findings of age-related dedifferentiation in human fMRI on the other hand, there is one missing piece of considerable importance. The results on the single-unit level I presented above are based on cell-specific tuning functions. The extraction of these tuning functions relies on a quantifiable similarity between presented stimuli along a continuous dimension. The rotation of a bar or the direction of an object's movement (Schmolesky et al., 2000; Leventhal et al., 2003; Liang et al., 2010) are good examples to illustrate this: in this case, the similarity between two stimuli is given by the angle between them. Carefully manipulating stimuli along the continuous similarity space of angular distance and measuring a neuron's firing allows us to see how the cell's response changes as a function of similarity and, ultimately, how this relationship might be altered by progressing age. In contrast to this, studies conducted in humans have previously investigated age-related ND by applying category-focused approaches. Participants are usually shown different exemplars of categories, most prominently faces or scenes. ND has then been formalized *across* different categories (category-based, J. Park et al., 2012; Du et al., 2016; Koen et al., 2019) or *within* the same category (item-based, Goh et al., 2010; Trelle et al., 2019). However, what both of these have in common is that the similarity between different exemplars, unlike the rotation of a bar, are hard to quantify. Similarity measures between two different houses or faces are highly dimensional. While we can turn a bar by five, ten, and then 15 degrees, theses quantifiable steps are not possible when showing a participant different faces[4]. Despite its importance for connecting the work done in animals and humans, evidence for age-related ND over continuous spaces in humans is still lacking.

We heard so far that one of the most outstanding changes humans are confronted with in older age is the decline of memory function. The search for correlates in the aging brain has, apart from alterations in its structure, identified changes in the brain's functional aspects, some of which are considered to take a compensatory role. Neural dedifferentiation, the phenomenon

[4]One could think of a quantifiable similarity measure between, for instance, different faces. However, it would potentially have to span all possible dimensions a face could vary over. Additionally, not all of these dimensions might be equal in how strongly they influence the perceived similarity of two exemplars.

that neural signals in the aging brain exhibit decreased specificity, has been shown to interfere with memory performance and is a promising target in the quest to understand memory aging. Results in the search of the potential mechanisms behind neural dedifferentiation come from animal work, showing that some neurons are tuned to a broader range of stimuli as animals reach senescence. The category-based approaches used to investigate age-related ND in human fMRI have so far not provided evidence for specificity changes in neural representations of continuous space, like those used in animal research. Closing this gap and testing mechanistic hypotheses requires a new approach to investigate age-related ND in human fMRI, one that compares neural representations over one continuous variable. The core work of this thesis (see *article I* and *article II*) have been dedicated towards this endeavor and, in this, have turned towards the domain of spatial cognition, a set of abilities that is concerned with perceiving, remembering, and acting upon continuous space.

1.4.1 Aging and Dedifferentiation of Spatial Navigation

Spatial cognition and the related ability of navigation take a special stance within this thesis. This is mainly due to two characteristics. Firstly, it offers a handle on the previously posed question of whether we can find evidence for age-related ND over a continuous variable. To successfully navigate an environment, individuals have to keep track of the direction they are moving in, the distance travelled, and remember their trajectory through space (Spiers & Barry, 2015). In turn, during spatial navigation the brain is confronted with the task of representing continuous characteristics of the three-dimensional euclidean space around the navigator. With this anchor to continuous spatial relationships, variables of navigation provide a way to deviate from the category-based approaches previously used in the fMRI-based investigation of ND. Secondly, and of note given the lifespan perspective of this thesis, spatial cognition stands out from other cognitive abilities due to its unique trajectory in lifespan development. Navigation abilities are heavily vulnerable to age-related decline (Moffat, 2009) and their assessment has proven useful in the early diagnostics of pathological aging (Moodley et al., 2015). The effects of age on the brain's capacity to represent continuous spaces will add to the understanding of special trajectory that the aging navigational system holds, and potentially inform its clinical application. On an additional note, findings related to how the brain of older adults represents continuous space might also be informative to domains of cognition less concerned with physical

space. Much research in the recent years has focused on how the principals with which the brain processes spatial knowledge might also apply to more abstract content and serve as a more general way to organize information (see Behrens et al., 2018; Tolman, 1948).

Staying within the spatial domain, what exactly these principles are and how the brain manages to overcome the complex challenge of way-finding has been a subject of research for over 70 years. When examining navigational behavior in rats, Tolman, Ritchie, and Kalish (1946) obstructed heavily learned paths towards a rewarded goal location. What they observed was that, even though the usual path had been blocked, the animals were able to take alternative routes to reach the reward location. Their account as to why the rats were able to show this behavior was that they are taking advantage of a so-called *cognitive map*, an organized, map-like knowledge of the animal's environment that reflects the continuous relationships of space. Neuroscience has since then made great advances towards understanding the mechanisms that allow the construction of this cognitive map, the potential basis of our ability to navigate, and how the brain might code its important cornerstones: variables like location, distance, and direction (for a review, see Grieves & Jeffery, 2017). Regarding the neural coding of space, animal work was able to identify a plethora of specific cell types responding to different aspects of our environment that are thought of as the cognitive map's building blocks. The most prominent ones are so-called place cells and grid cells. Place cells, first reported and most commonly located in the hippocampus, were found to code specific locations in an environment explored by freely moving rodents (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978). Grid cells, identified in the rodent's entorhinal cortex several years later, exhibit similar response fields. However, unlike place cells, each cell fires in multiple locations that tile the environment in a systematic, hexagonal lattice (Fyhn, Molden, Witter, Moser, & Moser, 2004; Hafting, Fyhn, Molden, Moser, & Moser, 2005). Together, place cells and grid cells are hypothesized to provide information about an animal's location, travelled distance, and to span a type of coordinate system in a certain space (Rowland, Roudi, Moser, & Moser, 2016; McNaughton, Battaglia, Jensen, Moser, & Moser, 2006; Mathis, Herz, & Stemmler, 2012; Moser, Moser, & McNaughton, 2017). Research identified a plethora of other cell types that have been demonstrated to code for numerous variables of space (see Behrens et al., 2018), such as the distance to walls or targets (Sarel, Finkelstein, Las, & Ulanovsky, 2017; Solstad, Boccara, Kropff, Moser, & Moser, 2008; Lever, Burton, Jeewajee, O'Keefe, & Burgess, 2009), travelling speed (Kropff, Carmichael,

Moser, & Moser, 2015), or the location of other animals (Danjo, Toyoizumi, & Fujisawa, 2018).

Head direction cells are tuned to the continuous space of physical orientation in the environment

Besides the computation of one's location and distance to potential targets, successful navigation also requires a sense of direction (Rosenbaum, Spiers, & Bohbot, 2018). An accurate coding of direction is a critical component of the navigational system and plays a key role in *path integration*, the ability to internally combine cues of linear and angular self motion to track one's position in space (McNaughton et al., 2006; Etienne & Jeffery, 2004). Direction differs from other spatial variables like location and distance in that its metric is angular. It is therefore not only continuous in nature but at the same time circular, meaning that there are no boundaries to its space. As an example, a navigator that, while standing still, consistently turns into the same direction will eventually again approach its original starting orientation. When we think back to the animal work that identified neural broadening as a potential mechanism behind ND, the rotating bars Schmolesky et al. (2000) used to investigate these age-related differences in neural tuning share the same characteristics. With the goal of addressing the gap between animal and human work and investigating ND over continuous spaces, spatial orientation therefore offers a promising variable.

Adding to this, the similarities also expand into the neural substrates needed to encode spatial orientation. Adding to other specified cell-types involved in navigation, Taube, Muller, and Ranck (1990a) discovered neurons with firing patterns that were tuned to the facing direction of freely-moving rats. The tuning curve of these so-called *head direction (HD) cells*, similar to the orientation-selective cells found in V1 investigated by Schmolesky et al. (2000), was bell-shaped and exhibited the highest firing rates at a cell-specific preferred facing direction of the rat. This directional tuning is aligned to an *allocentric* reference frame, meaning it is relative to stable landmarks in the environment. A rotation of these landmarks leads to a corresponding shift in a cell's preferred direction (Taube, Muller, & Ranck, 1990b; Taube & Burton, 1995). In fact, without visible landmarks HD cells are subject to an accumulation of error, exhibiting a less accurate representation of the animal's head direction over time. To avoid this drift and retain a stable directional signal, the system repeatedly anchors itself to stable landmark cues. Understanding these characteristics and how the HD system integrates

the firing of numerous individually tuned cells, vestibular, and visual information in order to create a sense of direction has been a great effort of animal work. This resulted in detailed models of the HD system that have so far found substantial neurophysiological support but will not be discussed here (for reviews, see Knierim & Zhang, 2012; Angelaki & Laurens, 2020)[5]. While in insects the neural substrates of such models are fairly centralized (Angelaki & Laurens, 2020), in mammals HD cells can be found more distributed, across the limbic system and in cortical areas. Reported sites include the subiculum, the antero-dorsal nucleus of the thalamus, the mammillary bodies, and the retrosplenial cortex (Taube, 2007; Winter & Taube, 2014).

In the context of human work, one question that arises is if it is possible to measure direction signals using fMRI. While the animal work on the single-unit level constructs a promising basis to investigate ND over a continuous space, the possible measurements applicable to the human brain are much more coarse. Addressing this question, Shine, Valdés-Herrera, Hegarty, and Wolbers (2016) combined immersive virtual reality (VR) in humans with subsequent fMRI to see if there was a measurable signal of differing allocentric direction in key areas of the HD system. They showed that this was indeed possible, presenting evidence that signals in the retrosplenial cortex (RSC) and thalamus, both areas exhibiting populations of HD cells in rodents (Winter & Taube, 2014; L. L. Chen, Lin, Green, Barnes, & McNaughton, 1994; L. L. Chen, Lin, Barnes, & McNaughton, 1994; Cho & Sharp, 2001), coded for direction in the global reference frame of the virtual environment. Similar results were found in a comparable study showing measurable signals of allocentric goal direction, also in human fMRI (Shine, Valdés-Herrera, Tempelmann, & Wolbers, 2019). Direction, in the context of spatial navigation, is therefore not only a promising target due to its parallels with ND-related animal work, like continuity and tuning. It is also a promising target because previous work has shown that neural representations of direction can be assessed in humans via non-invasive neuroimaging.

[5]For the interested reader: Predominant models take the form of a *continuous ring attractor* (McNaughton, Chen, & Markus, 1991). Attractor models describe systems in which neighbouring states are drawn towards an equilibrium point. In the case of direction there exist an infinite amount of these points which are conceptually arranged on a ring-like structure. Each particular equilibrium of the system reflects a certain direction. For more detail on the neural substrates of this model, see Angelaki and Laurens (2020).

Aging strongly affects navigation skills and spatial memory

When it comes to aging, studies have shown that spatial and navigational skills, relying on an accurate sense of direction, are among the most severely affected in older age (for reviews, see Moffat, 2009; Lester, Moffat, Wiener, Barnes, & Wolbers, 2017), a finding that is also reflected in the subjective reports of older adults (Burns, 1999). Behavioral performance in navigation tasks is strongly decreased in older individuals, with similar patterns in other species like rodents (Barnes, 1979) or non-human primates (Rapp, Peter R.; Kansky, Mary T.; Roberts, 1997). One of the most simple assessments of navigation ability are path-integration tasks. Here, participants start from a particular location and are either passively transported or asked to walk to two subsequent locations, usually including a slight turn. The task then consists in walking back to the starting location. To achieve this, participants have to integrate information about the travelled path and accurately estimate the required turn and distance. The participant's final position can then be compared to the starting location, offering a performance measure (e.g. see Harris & Wolbers, 2012). In these tasks, older adults' final locations have been shown to be less precise compared to younger adults across a variety of different conditions, including when performed in the real world or in VR (G. L. Allen, Kirasic, Rashotte, & Haun, 2004; Adamo, Briceño, Sindone, Alexander, & Moffat, 2012). The consistency of these age effects and the reliance of navigational skills on the MTL (Ekstrom et al., 2003) have sparked an interest in using such tasks in the diagnosis of certain neuropathology, for instance Alzheimer's disease (AD), that are known to impact structures in the MTL (for a review, see Coughlan, Laczó, Hort, Minihane, & Hornberger, 2018). Tests of episodic memory, the common method in the assessment of dementia (Dubois et al., 2014), are very practical in a clinical setting but require multiple assessments to separate healthy aging from the pathologically accelerated decline seen in dementia. Furthermore, other types of dementia with separate disease profiles manifest in similar memory-related symptoms. Studies have shown that assessments of navigational performance outperform those of episodic memory when having to distinguish AD from other forms of dementia (Tu et al., 2015; Yew, Alladi, Shailaja, Hodges, & Hornberger, 2012). Moreover, evidence suggests that they further enable differentiation of patients with mild cognitive impairment into high- and low-risk groups for the development of AD (Howett et al., 2019).

Besides the ability to precisely navigate, age-related decline has also been reported in tasks of spatial memory (Moffat & Resnick, 2002; Holden & Gilbert, 2012; Schuck et al., 2013; Schuck, Doeller, Polk, Lindenberger, & Li, 2015). An often applied test of spatial memory requires participants to remember specific allocentric locations in a virtual environment that displays proximal and distal cues. It has repeatedly been shown that in these tasks, compared to younger adults, older adults tend to rely more on egocentric strategies, where locations are encoded in reference to a proximal cue, rather than allocentric strategies that focus more on distal cues and boundaries of the environment (Schuck et al., 2013, 2015). Egocentric strategies, however, often lead to more errors, especially in non-static environments (Rodgers, Sindone, & Moffat, 2012; Wiener, de Condappa, Harris, & Wolbers, 2013). In a study by Schuck et al. (2015), older and younger participants had to remember the location of several objects in a 3D desktop VR of a circular arena. The arena offered distal landmarks such as mountains and clouds at its boundary and a proximal landmark within the arena in the form of a traffic cone (see Doeller, King, & Burgess, 2008; Doeller & Burgess, 2008). After an initial encoding phase, participants had to recall object locations from memory and navigate towards them. Older adults showed worse spatial memory performance compared to younger adults by placing objects further away from their correct location. Furthermore, older adults exhibited less improvement over time from provided feedback. To more thoroughly analyze the participants' strategies, in the final phase of the task the authors separately manipulated the size of the arena's boundary and the location of the proximal cue. They then predicted how participants would update their encoded object locations, either based on the shifted proximal cue (egocentric) or re-sized boundary (allocentric). Results showed that the indicated object locations of older adults were more in accordance with an egocentric model, while younger adults predominantly followed the allocentric approach.

Potential role of neural dedifferentiation in the spatial domain

What makes the study by Schuck et al. (2015) especially relevant for this thesis is that it presented evidence for a potential role of ND in spatial memory. A well-established finding in the literature of rodent and human spatial navigation is that allocentric processing relies more on structures in the MTL, especially the hippocampus, while landmark-based approaches are more related to responses in the striatum (McDonald & White, 1994; Packard & McGaugh,

1996; Doeller & Burgess, 2008; Doeller et al., 2008; Bird, Capponi, King, Doeller, & Burgess, 2010). While this pattern of specific processing was supported by fMRI results in younger adults, landmark processing in older adults was accompanied by increased activity in the right hippocampus. This argues for less differentiated processing of spatial information in older adults.

Although these findings are best described as category-based ND, they support the idea that aging also influences the specificity of cognitive processes in the context of spatial cognition. That similar patterns of ND (i.e. decreased specificity) might also be expected over the continuous space of direction has been indicated in a study by Stangl, Kanitscheider, Riemer, Fiete, and Wolbers (2020). They investigated the sources of age-related changes in navigation ability more closely by using computational modelling of extensive path-integration data. This allowed comparison between different possible sources of error, including internal noise of the integrator, misestimation of velocity, and a leaky integration process due to memory decay. Their results suggested that internal noise was by far the strongest error component for the estimation of one's position. This marks a parallel to computational models of ND that named a decreased signal-to-noise ratio as a key factor in the loss of neural specificity (Li et al., 2001). Adding to this, the authors reported decreased task performance in the older age group, similar to previous assessments (Mahmood, Adamo, Briceno, & Moffat, 2009; Bates & Wolbers, 2014). However, the only significantly different error component between age groups was the magnitude of internal noise, speaking in favour of an age-related affect on signal specificity. Regarding the source of this noise, the experimenters could show that errors increased with travelled distance, rather than time passed, suggesting that internal noise likely stems from sensory inputs during navigation, for instance visual and vestibular information. Both of these sources are relevant for an accurate signal in direction-selective cells (Winter & Taube, 2014) and are furthermore innervating neurons in MT that are subject to neural broadening with age (Liang et al., 2010), a suggested mechanism underlying ND.

To summarize, an open question in the literature of age-related ND is if specificity changes in neural signals can be found over continuous spaces. That this question has not been answered presents a disconnect between animal research on the mechanisms behind ND, which suggests that response patterns of cells become less selectively tuned to continuous variables, and findings in human fMRI where specificity changes have been reported predominantly across dif-

ferent stimulus categories. Spatial cognition is based on continuous variables, with the specific variable of direction showing strong parallels to stimuli used in related animal research. It has been shown that signals of direction can be measured in fMRI (Shine et al., 2016) and computational models of navigation performance suggest that increasingly noisy signaling within the system contributes to performance differences between age groups (Stangl et al., 2020). Considering these findings, measuring neural signals over the continuous space of direction offers a promising opportunity to address the disconnect between animal and human work in age-related ND by comparing age groups regarding the specificity with which the brain can represent the continuous space of direction.

1.4.2 Non-spatial continuity: Aging and outcome-based learning

So far, we have spoken about functional differences in the aging brain, specifically ND. We talked about how it is possible to address the open question of whether the age-related loss of neural specificity also impacts representations of continuous space. This is the main goal of *article I* and *II*, both of which investigate the spatial variable of direction. However, continuous variables are not only relevant in physical space. One domain that is inherently connected to continuity is value-based decision making. Value-based decision making provides a framework for the analysis and prediction of choices when an agent is confronted with different options. At the core of the framework is the idea that different choice options are judged based on a continuous and subjective value metric. Each of the agent's potential choices are assigned a conceptual value depending on its outcome and other situational factors, like the agent's motivational state or the probability with which an outcome occurs. This value metric allows for the comparison of different choice options and holds predictive power over an agent's behavior. In this sense, value has been the basis of many influential models of decision making (e.g. prospect theory, Kahneman & Tversky, 1979; Tversky & Kahneman, 1992) and learning (e.g. Rescorla-Wagner learning rule, Rescorla, 1968; Wagner, Logan, & Haberlandt, 1968).

The neuroscience of decision making has intensively investigated neural substrates of subjective value (see Glimcher, 2014). These investigations have shown that value provides a continuous metric not only conceptually; it is also represented in the brain. Strong evidence for neural representations of subjective value have been demonstrated, for instance, in the human ventro-medial PFC and ventral striatum (Clithero & Rangel, 2014). Supporting the

idea of a continuous value metric, these responses have been shown to scale with increasingly rewarding outcomes (Bartra, McGuire, & Kable, 2013). Furthermore, some value representations, most likely in the orbitofrontal cortex, are adaptive to the range of available rewards (Padoa-Schioppa, 2009; L. T. Hunt et al., 2012), potentially allowing the system to provide an equally detailed value metric across varying environments.

However, evidence for a continuous value metric in the brain does not imply that decision processes, especially in the face of risk, are rational and linear. Work on prospect theory (Kahneman & Tversky, 1979; Tversky & Kahneman, 1992) has shown that adults overweight events with low probabilities during decision making, and perceive relatively less gains with larger outcomes. Especially rare and extreme events that stand out among regularly encountered values, or those that are located at the edges of distributions have repeatedly been shown to introduce a bias into the decision making processes (Madan & Spetch, 2012; Madan, Ludvig, & Spetch, 2014; Ludvig, Madan, McMillan, Xu, & Spetch, 2018). It has been claimed that this relative overrepresentation of extreme events, in the face of associated cognitive demand and time, describes an optimal use of finite resources (Lieder, Hsu, & Griffiths, 2014; Lieder, Griffiths, & Hsu, 2018). More generally, research has shown that aging shapes decision making and learning with consequences for important aspects of everyday life like monetary and health-relate choices (Tymula, Rosenberg Belmaker, Ruderman, Glimcher, & Levy, 2013; Eppinger, Hämmerer, & Li, 2011). In the context of decisions, older adults are differently influenced by key characteristics of the available choices, like associated risk (Mata, Josef, Samanez-Larkin, & Hertwig, 2011; Best & Charness, 2015) and uncertainty (Nassar et al., 2016). With these findings in mind, Pachur, Mata, and Hertwig (2017) addressed the question of how extreme events are integrated into the decision process of older adults. They confronted a younger and older age group with different gambling problems, each offering a choice between two monetary lotteries. Each lottery was associated with two possible outcomes happening with a respective probability (e.g. lottery A: 50% to win 5$, 50% to win 1$; lottery B: 10% to win 30$ and 90% to win 0$). Using a computational model based on cumulative prospect theory (Tversky & Kahneman, 1992), the study found that both older and younger adults proportionally overweighted low probability events in their decisions. While this was true for both age groups, older adults did so to a stronger degree than younger participants, reflecting increased optimism about the

possibility of a gain[6].

Decisions from description, such as those investigated by Pachur et al. (2017), take an important role in the research of value based decision making. They provide participants with all necessary details about the outcomes and study decisions in the face of full information. Another approach is investigating decisions when participants have to collect necessary information themselves, usually referred to as decision from experience (see Hadar & Fox, 2009; Hertwig & Erev, 2009). This approach involves a period of sampling, where participants have to use trial-by-trial feedback to update their estimate of an option's value, an outcome-based learning process. In such cases, when participants have to build up their expectations about outcomes step-by-step, extreme outcomes are characterized by their associated surprise. This is expressed by the difference between the participant's expectation and the encountered outcome. In models of reinforcement learning (RL), learning processes are based on this difference, which is called the *prediction error* (Sutton & Barto, 2018). Estimates of future outcomes are then adjusted by the prediction error but weighted by a *learning rate*. Considering the findings of Pachur et al. (2017), also RL models could technically allow for an analogous overrepresentation of extreme or surprising events, specifically by increasing the learning rate for trials that offer surprisingly high or low value. But is this biased representation of a continuous outcome space together with its age-related difference a finding that generalizes from descriptive decision making towards learning processes? Are older adults learning more from surprising outcomes than younger adults? Moving away from physical space and towards the representation of abstract continuous space, the third work of this dissertation aims at addressing these open questions (see *article III*).

[6]Pachur et al. (2017) also included lotteries from the loss domain, where the participants gambled to avoid monetary losses. Patterns of probability weighting differed in comparison to the gain domain. Furthermore, in the loss domain there was no age difference in probability weighting, demonstrating the complex interactions between task framing, decision making, and age differences therein. For detail, see Mata et al., 2011 and Best & Charness, 2015.

2

RESEARCH QUESTIONS

The previous chapter provided a general background regarding the influence of age on memory, neural dedifferentiation, spatial navigation, and the representation of continuous spaces, neurally as well as behaviorally. Furthermore, it laid out a set of open questions, which this dissertation aims to address:

Question 1: Is there evidence for the age-related dedifferentiation of neural representations over a continuous space as measured by fMRI?

Previous investigations of age-related ND of human fMRI signals have been focused on categorical approaches (e.g., see D. C. Park et al., 2001; Carp, Park, Polk, & Park, 2011; Koen et al., 2019). These helped to establish robust evidence for reduced specificity of neural representations in older age and how this phenomenon might contribute to age-related memory impairment (Koen & Rugg, 2019). One mechanism suspected in the emergence of age-related ND stems from animal research showing that neurons in senescent monkeys tuned to orientations of a visual stimulus, a continuous variable, exhibit reduced specificity in the form of wider tuning functions (Schmolesky et al., 2000; Leventhal et al., 2003; J. Park et al., 2012). So far, no evidence has been provided for age-related ND over a continuous variable in humans, leaving open an important gap between findings in human fMRI and its suspected mechanisms. Further, continuous variables enable investigation of a system's tuning specificity. This can be used to not only assess *if* neural specificity changes with age, but also *how* it changes (see section 3.1). Addressing the gap between animal and human work and investigating the principles age-related ND might follow has been the main objective of *article I*. *Article II* extends this work.

Question 2: Can we provide causal evidence that reduced dopamine functioning in older age contributes to age-related neural dedifferentiation?

Computational models have suggested a role of the neuromodulator DA in the fidelity of neural representations (Li et al., 2001; Li & Rieckmann, 2014). In these models, reduced specificity of downstream neural signals arises from deficient levels of neural gain modulation, a potential

consequence of reduced DA functioning. Earlier work has shown that older age is associated with reduced D_2-receptor density (Wong et al., 1997; Y. K. Yang et al., 2003), limiting the neuromodulatory function of DA and hence underlining its potential role in the emergence of age-related ND. Direct evidence that levels of DA influence the neural specificity of fMRI-signals has not been provided. The work in *article II* has been conducted to investigate a causal relationship between the two. By using a similar approach, *article II* also allowed me to assess if the results in *article I* replicate in a different data set.

Question 3: How does age affect the way humans learn from extreme events?

Extreme events introduce a bias into our decision making process (Tversky & Kahneman, 1992; Ludvig et al., 2018), supposedly since they rationally reflect the most important potential consequences of our actions (Lieder et al., 2018). The strength of this bias is subject to age differences. Older adults, more than younger adults, overweight low-probability, extreme events when making decisions from description in the gain domain, reflecting increased optimism about the possibility of a large outcome (Pachur et al., 2017). Such an overrepresentation of extreme outcomes during decision making opens up the possibility of a similar, non-linear influence during learning. This is because surprise, often connected to extreme outcomes, takes a key role in trial-wise learning from feedback and influences subsequent decisions. Models of RL have contributed greatly to the understanding of said learning processes over the life course (Eppinger, Schuck, Nystrom, & Cohen, 2013; Samanez-Larkin & Knutson, 2014). In these models, a stronger weight on surprising events could manifest in increased learning rates in trials with high prediction errors. This framework allows me to tackle the actively debated role of surprising events in learning experiences and how it might change with age. This endeavor, the objective of *article III*, will help to further understand decision making processes in older adults.

Seeking answers to these questions is the main contribution of this cumulative dissertation, resulting in the completion of three independent research articles. Addressing the first two questions (see *article I* and *II*) required the development of a new analysis approach. As I consider this another important contribution of this dissertation, the following chapter will elaborate more on the applied methodology.

3

OVERVIEW OF INDIVIDUAL WORKS

3.1 General Methodology

As laid out in the previous chapters, a central goal of this dissertation was to more closely connect the findings of age-related ND in human fMRI and those of its potential mechanisms originating from investigations of cell tuning in animals. Achieving this relied on the investigation of age-related changes in neural specificity over a continuous variable. This variable was given by direction during the process of spatial navigation. Different directions are connected by a continuous, quantifiable distance metric, namely angular distance[7]. These conditions required the development of a new approach, which will be described in this section. A schematic of the approach is displayed in Figure 1. The procedure mainly offered two advantages compared to previous investigations. First, the continuous distance metric made it possible to go beyond previous measures of neural specificity. In particular, it allowed the construction of fMRI-level tuning functions for the space of direction. These express how similarity between neural representations changes with increasing angular distance of the corresponding directions. In doing so, they present a more principled measure of neural specificity. They provide information about the organizational principles of the underlying neural representations. For instance, they can help to distinguish if neural similarity equally differs between all directions or gradually decreases with larger angular distance. Furthermore, they differentiate if reduced specificity happens while such organizational principles are upheld or rather due to their deterioration. This is particularly valuable for the research of age-related changes, the main focus of this work. This information can be accessed by analyzing the shape of the fMRI-level tuning function. A decreasing similarity with increasing angular distance would, for example, be captured by a Gaussian shape. The width of a fitted Gaussian distribution would in this case give a measure of neural specificity. The second advantage was that the neural representations

[7]To illustrate: the angular distance between the allocentric orientation of 120° and 180° equals 60°. It therefore takes a turn of 60° to transition between both directions. Since the space of direction is circular it has no boundary. In turn, when considering the shortest connection between two points the maximum angular distance is 180°. Under this premise, the angular distance between the allocentric directions of 300° and 60° equals −120°, not 240°.

of direction were extracted from free roaming during a spatial memory task. The approach is therefore easily adaptable to other data sets that include similar conditions (free navigation while undergoing neuroimaging). Specifically *article II* made use of this characteristic.

I implemented the described approach in *article I* and *II*. Both publications analyzed paths travelled during a desktop VR spatial memory task completed by older and younger adults whilst undergoing fMRI. The tasks allowed participants to freely move around a circular arena with the goal of navigating to a number of object locations that had to be retrieved from memory. To extract neural representations of different directions, each participant's travelled paths were first calculated from the frequently logged position and azimuth within the arena. To obtain high fidelity neural representations, we only analyzed episodes of active walking in a certain direction. The resulting paths were therefore separated into events of consistent forward walking within the same direction. The collected imaging data then allowed the extraction of neural signals in response to the isolated events of different walking directions. To ensure enough events for each direction, the allocentric 360° space was discretized into six, equally sized bins of 60°. This resulted in a set of neural representations of different directions which, in contrast to previous category-based approaches, reflected a continuous, circular space.

Individual measurements of participants' neural specificity and tuning were operationalized using a multivariate pattern classifier (see Carp et al., 2010; Carp, Park, Hebrank, et al., 2011; Carp, Park, Polk, & Park, 2011). The classifier was trained on neural patterns of the different binned walking directions (0°, 60°, 120°, 180°, 240°, 300°). In a testing set of never-before-seen neural patterns, the classifier then predicted individual participants' walking direction. To extract fMRI-level tuning functions we extended the analysis to the classifier's confusion matrix. The confusion matrix entails how often the classifier predicted each class given the true class it should have predicted. This allowed me to investigate how neural similarity (measured by the frequency of the classifier's mistakes) changes as a function of stimulus similarity. An example: when the true class is 60° the false prediction of the neighbouring direction (120°) might come up more often than the polar opposite direction (300°). This would suggest that similarity of neural patterns is higher between neighboring directions (60° and 120°) and decreasing as the angular distance between directions increases (60° and 300°). To quantify this relationship, confusion matrices were converted into fMRI-level tuning functions by expressing all predictions based on their angular distance to the target class (-120°, -60°, 0°, 60°, 120°, 180°). I specifically

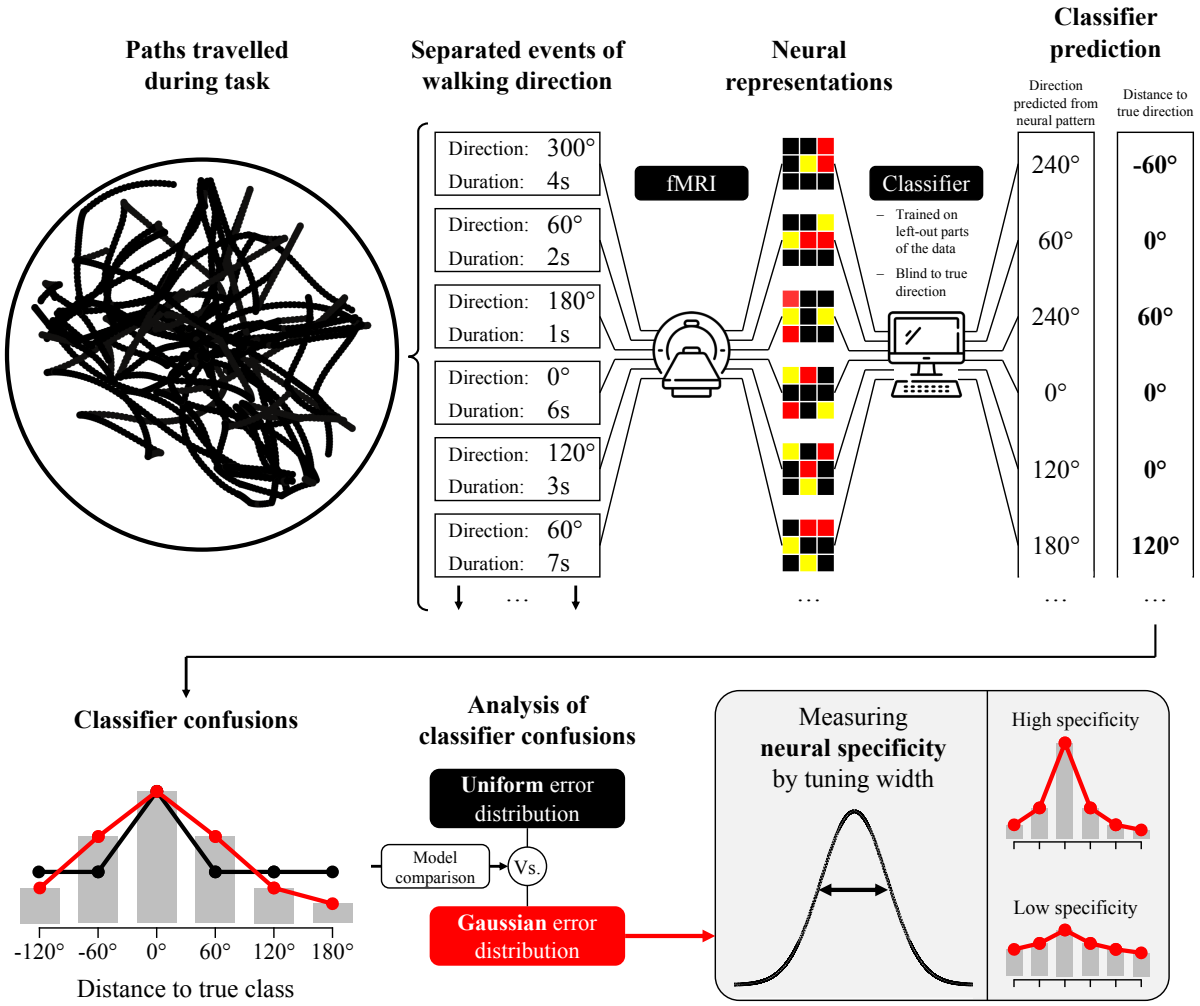

Figure 1. Schematic of analysis procedure for *article I* and *II*. During the task participants freely navigated a 3D VR while completing a spatial memory task (see top left). Highly frequent logging of a participant's position and azimuth allowed the reconstruction of individual paths. These paths were separated into events of consistent walking into a specific direction (six directional bins with 60° width; duration $>$ 1s). Simultaneous recording of fMRI allowed the isolation of neural representations of walking direction events. A classifier was trained on separated parts of the data to predict participants' walking direction from the corresponding activation pattern. Its predicted directions from a held-out set of neural data were then compared to ground truth. The angular distance between the target direction and the predicted direction (see top right) were contained in the confusion matrix. The classifier's predictions could therefore be expressed by the angular distance to the target direction (see bottom left). The frequency of a 0° distance corresponded to a correct prediction and, in turn, in relation to the number of all predictions measured classification accuracy. Distances other than 0° were errors of which their frequency stands in direct relation to the underlying neural similarity between target class and predicted class. Therefore, the distribution of errors contains information about the underlying organizational principles with which direction is represented in the brain. Error distributions were tested with a model comparison (Gaussian: closer in space equals higher neural similarity; Uniform: all directions are equally [dis-]similar to each other). The shape of the fitted curves gave a more principled measure of neural specificity containing information of the entire space. In the case of a Gaussian error distribution this was expressed in measures of dispersion (tuning width, see bottom right).

chose to investigate neural similarity based on classifier judgments since it comes close to the problem posed to downstream brain areas which have to read out population-level tuning functions (Jazayeri & Movshon, 2006; Averbeck, Latham, & Pouget, 2006).

I compared two models of the tuning function. First, a Gaussian curve inspired by tuning functions found in the animal literature (Schmolesky et al., 2000; Leventhal et al., 2003; Liang et al., 2010) where false predictions (i.e. neural similarity) decrease with larger angular distance to the target class. Second, a model that assumed no such relationship and therefore equal distribution of false predictions among all non-target classes. In areas that showed evidence of a Gaussian relationship, neural specificity could be assessed by the width of the fitted Gaussian curve. More narrow curves postulate a quick decrease in neural similarity with even small differences between underlying stimuli, corresponding to higher neural specificity. Furthermore, an additional, more general measure of neural specificity was reflected in the amount of the classifier's correct predictions, measuring how distinguishable the patterns of each direction were from every other direction. In order to asses age-related ND older and younger adults were compared based on both measures. To investigate the role of neural specificity of direction representations in spatial memory, the measures were also related to task performance.

While a similar approach was used for both *article I* and *II*, its implementation was slightly different. The largest difference consisted in the extraction of neural representations of walking direction and the applied classifier. In *article I*, neural representations of walking direction were extracted based on a general linear model (GLM) with individual regressors for each binned walking direction. A classifier in the form of a linear support vector machine then operated on the resulting beta maps. Due to circumstances introduced by its specific drug-intervention design in *article II*, I applied a linear regression classifier that operated directly on the neural patterns associated with a travelled direction. *Article III* aimed to investigate behavioral data in a decision making task. Since the methods are unique to *article III* they are best described in its summary below.

3.2 Summary of individual works

The present thesis addresses the questions outlined in the previous sections through three research articles. *Article I* exhibits the first account of measuring ND in the context of a

continuous, spatial variable, namely walking direction. ND has previously only been shown in the context of categorical variables. This study aims to answer open questions not only about the presence of age-related changes in neural specificity of continuous variables but also about the specific form these changes may take. *Article II* builds upon the foundation of *article I*, with the aim of evaluating decreased DA functioning as a candidate mechanism behind age-related ND. Decreased DA functioning in older age has been proposed to influence neural specificity due to a limitation in the transmitter's neuromodulatory effect (Li et al., 2001; Bäckman, Lindenberger, Li, & Nyberg, 2010; Li & Rieckmann, 2014). To examine this, it applies a similar spatial paradigm as in *article I*, combined with a double-blind, within-participant Levodopa (L-DOPA) drug intervention design that allows causal conclusions about the role of dopamine in age-related ND. Finally, *article III* shifts the perspective away from spatial paradigms and towards the more abstract, continuous space of outcomes in a RL task. The study applies computational modelling of RL to identify differences in the ways older and younger adults update expected reward of their choices, specifically when confronted with rare and surprising outcomes.

All work related to the articles was conducted within the Max Planck Research Group "Neural and Computational Basis of Learning, Decision Making and Memory (NeuroCode)", led by Dr. Nicolas W. Schuck at the Max Planck Institute for Human Development in Berlin, Germany. Funding was provided by an Independent Max Planck Research Group grant awarded to Dr. Nicolas W. Schuck by the Max Planck Society (M.TN.A.BILD0004). Furthermore, the International Max Planck Research School on the Life Course (IMPRS-LIFE) supported this work in the form of a fellowship.

Article I: An fMRI study to investigate age-related neural dedifferentiation over the continuous space of walking direction

Koch, C., Li, S.-C., Polk, T.A., & Schuck, N.W. (2020). Effects of aging on encoding of walking direction in the human brain. *Neuropsychologia*, *141*, 107379. doi: 10.1016/j.neuropsychologia.2020.107379

The goal of this fMRI study was to investigate age-related ND in the context of a continuous variable to gain further insight into the phenomenon's mechanisms. The appropriate framework

was provided by spatial cognition, a domain with a special stance among aging research which offered the suiting variable of walking direction.

Theoretical Background

One potential mechanism behind age-related ND is that neurons with narrow tuning to a preferred stimulus in older age widen their spectrum of preference, effectively responding to a broader range of stimuli. This idea is based on electrophysiological recordings showing that senescent monkeys exhibited broader tuning curves of V1 neurons responding to the orientation of a stimulus (Schmolesky et al., 2000; Leventhal et al., 2003). While this idea of neural broadening in humans has since been supported with fMRI (J. Park et al., 2012), its evidence together with findings of age-related ND in general stems from increased pattern similarity across separate visual categories (e.g. faces and houses, see D. C. Park et al., 2004; Voss et al., 2008; Burianová, Lee, Grady, & Moscovitch, 2013; Carp, Park, Polk, & Park, 2011). Within a single, continuous domain, however, there has been no evidence to date for age-related ND as measured by fMRI. One cognitive domain inherently relying on continuous information, for example visual and directional information, is spatial navigation. In order to build a closer link between human and animal literature, *article I* therefore investigates age-related dedifferentiation of neural representations of different walking directions during virtual navigation. The specificity of neural responses has furthermore been linked to encoding and retrieval of memory content (Zheng et al., 2018; Koen & Rugg, 2019). Therefore, this approach also offers an additional perspective to further understand older adults' particularly pronounced memory impairments in the spatial domain (Moffat, 2009; Lester et al., 2017).

Methods

I re-analyzed data of 43 participants (24 younger adults, 19 older adults) facing a 3D desktop VR spatial memory task while undergoing fMRI, originally published in Schuck et al. (2015). To obtain measures of neural specificity for each participant, I applied the analysis approach laid out above in section 3.1. A support vector machine was used for classification. It operated on direction-specific beta maps resulting from a GLM that included regressors for each direction bin. Beta maps were extracted for a set of predefined regions of interest (ROIs) associated with visual and spatial signals and a motor cortex control. In areas that allowed above-baseline

classification of direction I further analyzed the classifier's confusion matrix to construct fMRI-level tuning functions. If the model comparison confirmed that the resulting tuning functions within a ROI followed a Gaussian shape, I analyzed the width of the fitted Gaussian curve. To assess age differences in neural specificity in the respective ROIs I compared both measures of neural specificity between age groups.

Besides the assessment of age-related ND, a set of additional analyses were performed. These included an investigation of the relationship between task performance and the reported measures of neural specificity to assess its involvement in spatial memory. Furthermore, in a number of additional tests I studied potential influential factors on the tuning function. Specifically, I evaluated the influence of a smaller bin size of the directional space as well as the role of visual information. Regarding the latter, I assessed the similarity of the visual input associated with different directions using a biologically plausible model of the visual stream (HMAX; Riesenhuber & Poggio, 1999; Serre & Riesenhuber, 2004). I then related differences in visual similarity between directions to differences in the similarity of their respective neural representations. Moreover, I analyzed drops in classifier performance when visual information and walking direction mismatched during periods of backwards walking. Assessing if a trained classifier picks up more on the travelled direction (backward) or the viewing direction (forward) allowed quantification of how strongly direction signals were driven by visual information. All code related to *article I* can be found at https://github.com/koch-means-cook/direction_decoding.

Major Findings

The results present evidence for age-related ND in the context of the continuous variable walking direction. Data from the early visual cortex (EVC) and retrosplenial cortex (RSC), areas in which direction could be decoded above a motor control baseline, suggested that neural specificity as measured by classification accuracy was reduced in older adults. In the RSC, an area which has previously been linked to direction signals (Shine et al., 2016), this measure also correlated with participants' behavior, wherein lower neural specificity was associated with worse task performance. Furthermore, our new approach unique to continuous spaces (see section 3.1) investigated tuning across the entire space of direction. This produced two important results inaccessible to previous approaches. Firstly, tuning functions of both areas

were better explained by a Gaussian model, meaning that pattern similarity gradually decreased with the angular distance between the underlying directions. Secondly, analyzing the shape of the Gaussian curves fit to individual tuning functions showed that early visual cortex (EVC) tuning functions were broader in older adults, while there was no age difference in the RSC. These findings suggest that the similarity of neural representations reflects their relationship in space. Moreover, related specificity changes in older age are less likely to be related to the deterioration of these organizational principles. Rather, the similarity structure is maintained but, in the case of the EVC, less precise in older adults.

Article II: An fMRI study to investigate the role of dopamine as a potential mechanisms behind age-related neural dedifferentiation of walking direction

Koch, C., Baeuchl, C., Glöckner, F., Riedel, P., Petzold, J., Smolka, M.N., Li, S.-C., & Schuck, N.W. (2022). L-DOPA enhances neural direction signals in younger and older adults. *NeuroImage*, *264*, 119670.
doi: 10.1016/j.neuroimage.2022.119670

Building upon the findings of *article I* this drug intervention study investigated a potential, physiological mechanism behind age-related ND: changes in the availability of the neurotransmitter dopamine (DA).

Theoretical Background

Older adults show reduced DA functioning, supposedly with negative consequences for cognition (Volkow et al., 1998; Chowdhury et al., 2013; Li, Lindenberger, & Bäckman, 2010; Bäckman et al., 2010). When the neuromodulatory effects of DA decline, computational models suggest this is expressed in a diminished signal-to-noise ratio and therefore lowered specificity of neural responses (Cohen & Servan-Schreiber, 1992; Li & Rieckmann, 2014). With this link to neural specificity, DA therefore offers a potential mechanism for the emergence of ND. *Article I* presented evidence for age-related ND over direction-selective fMRI signals in the context of spatial navigation. This fMRI study aims to investigate a causal link between the specificity of direction-specific signals and levels of DA in younger and older adults.

Methods

I analyzed fMRI data of 80 participants (37 older adults, 43 younger adults) completing a paradigm similar to that of *article I* but embedded in a double-blind cross-over drug intervention design. Each participant completed two sessions of the task, once under the influence of a Placebo, and once under the influence of L-DOPA, a DA precursor. I again trained and tested a classifier to decode walking direction from participants' fMRI patterns using a similar analysis approach described in section 3.1 and *article I*. The procedure was adjusted to yield separate measurements for the Placebo and L-DOPA session. This allowed a direct, within-participant comparison of the drug's effect on the neural specificity of direction-specific signals. Measures again included classification accuracy and tuning width in a set of predefined ROIs. Furthermore, I analyzed drug effects on spatial memory performance as well as its relationship to drug-induced changes of neural specificity. This article applied a reproducible and standardized pre-processing of fMRI data using *fMRIprep* (Esteban et al., 2019; software version 20.0.6, Esteban et al., 2020). Due to the L-DOPA administration, I further used the *MRIQC* software (Esteban et al., 2017) to obtain estimates of participant motion during fMRI image acquisition and to apply them as nuisance variables during statistical modelling. All code related to *article II* was made publicly available at https://github.com/koch-means-cook/damson.

Major Findings

The administration of L-DOPA showed an enhancing effect on the neural specificity of fMRI patterns associated with walking direction over the set of investigated ROIs. This speaks in favor of a causal role of L-DOPA for neural specificity in the context of spatial navigation. Exploratory follow-up analyses showed that the hippocampus exhibited the strongest effect of L-DOPA which was also independent of age. In the RSC, enhancing effects of L-DOPA administration were exclusive to the younger adults. Tuning width, however, did not show any drug-induced changes. Moreover, the study was able to replicate the findings of *article I*, demonstrating that older adults exhibited generally lower neural specificity as well as wider tuning functions, both in the EVC.

Article III: A behavioral study to investigate age-related differences in learning from a non-spatial continuous space

Koch, C., Zika, O., & Schuck, N.W. (2022). Influence of surprise on reinforcement learning in younger and older adults. *PsyArXiv*.
doi: 10.31234/osf.io/unx5y

Continuous spaces are also present in our daily lives outside the spatial domain. This work investigates age-differences when learning from the more abstract continuous space of rewards in a reinforcement learning task.

Theoretical Background

Studies have found age differences in the domain of risky decision making (Best & Charness, 2015) and learning from feedback (Samanez-Larkin & Knutson, 2014). One particular finding is that, compared to younger adults, older adults react differently to choices involving extreme or surprising values drawn from the edges of continuous reward spaces (e.g. points or monetary values; Best & Charness, 2015; Mata et al., 2011; Pachur et al., 2017) with studies painting a complex picture of stronger over- or underweighting of such outcomes in the decision process of older adults. While RL offers a promising perspective for understanding these findings, the question of how outcome-based learning from surprising values might change over the lifespan remains open. The present study addresses this question by investigating how younger and older adults over- or underweight outcomes that elicit large prediction error (PE)s in an RL framework.

Methods

We analyzed data of 102 participants (51 younger adults, 51 older adults) completing an online value-based learning task. The task involved pairwise comparisons of three bandits, one of which occasionally produced surprising outcomes (i.e., large PEs). The outcome distributions of the involved bandits were set so that overweighting of surprising outcomes would show itself in erroneous decisions. Besides comparing both age groups on how these surprising outcomes might influence individual choices, I also applied computational modelling to gain further insight to the involved learning process. To capture different weighting of surprising outcomes we tested a model that allowed a participant's learning rate (LR) to scale with the

encountered PE in a given trial. This enabled stronger (or weaker) updating in the case of large PEs, a consequence of surprising outcomes. A comparison to other candidate models, e.g. one incorporating uncertainty, was conducted to see which model best explained participants' choices and if this differed between younger and older adults. All code related to *article III* can be found at https://github.com/koch-means-cook/pedlr.

Major Findings

Behavioral analyses showed that older adults, compared to younger adults, had longer reaction times and more erroneous decisions in the bandit pair affected by surprising outcomes. Furthermore, when asked to estimate potential outcomes of their choices, older adults showed stronger distortion of their estimates towards the direction of the surprising outcomes. When approaching behavioral patterns of participants with different computational models, a model that allowed for differential weighting of surprising outcomes (*Surprise* model) explained the data best across all participants. Interestingly, age groups did not differ in which model offered the most accurate account of participants' choices, nor in the winning *Surprise* model's parameterization. Overall, the findings indicate that both older and younger adults differentially weight surprising events producing large PEs in their decision process. As evident in participants' choices and outcome estimates, older adults seem to overweight surprising outcomes during learning more strongly compared to younger adults. This presents evidence that the continuous space of PEs is encorporated differently in the decision making process of older adults.

4

GENERAL DISCUSSION

In this final chapter, I will first quickly summarize the main results across the three presented articles. The reported findings will then be discussed in the light of previous research, followed by a closer look at their limitations. Finally, I will broaden the perspective and focus on potential future work that could follow the presented articles. The thesis will then close with a set of concluding remarks that consider its overarching goal.

4.1 Summary and evaluation

The general aim of this thesis was to understand how aging shapes neural representations, specifically of continuous spaces. One particular functional change described in the aging brain is neural dedifferentiation (ND), a loss in the specificity with which it is able to represent information, perceptual or conceptual (Koen & Rugg, 2019). In this context, continuous spaces have not received enough attention, especially when considering their role in the research on the potential mechanisms behind ND. To address this disconnect, two of the articles in this thesis applied a novel approach to measure age-related ND over a continuous space, namely walking direction in a virtual environment. The results of these works showed that different walking directions were harder to classify based on their neural representations in older compared to younger adults, specifically in early visual areas. Further, the continuous space of direction offered the particular advantage of an underlying continuous and quantifiable distance metric between stimuli (i.e. angular distance). This allowed the assessment of fMRI-level tuning functions. In the early visual cortex (EVC) and retrosplenial cortex (RSC), these tuning functions were best described by a Gaussian curve. This corresponded to a gradual decrease in neural similarity with larger angular distance of the underlying directions. This was true for younger as well as older adults. However, in early visual areas the precision of the fitted Gaussian was lower in older adults, suggesting higher similarity between neural representations related to neighbouring directions.

The L-DOPA drug intervention-design of the second work allowed for additional findings, specifically related to the causal influence of DA functioning— a candidate mechanism behind

ND (Li et al., 2001; Li & Rieckmann, 2014). The administration of the DA precursor statistically increased the accuracy of a walking direction classifier across the investigated regions. This drug related enhancement was present in older as well as younger adults.

Finally, to provide a wider perspective about the influence of age on representations of continuous spaces, *article III* moved into the field of RL. It investigated how younger and older adults diverge in learning from continuous outcomes and representing them in their decision process. Model comparisons of participants' behavior showed that choices of both age groups were best explained by a model that reflected differential influence of surprising events on participants' choices, rather than uncertainty. Behavioral results, however, revealed that surprising outcomes had stronger immediate effects on older adults' choices and reward estimates, specifically on decisions that immediately followed large, surprising prediction errors.

Age-related neural dedifferentiation over a continuous variable

The main question that led to *article I* was if there is evidence for age-related ND over a continuous variable. This endeavor was motivated by a disconnect between human work and studies in animals that identified neural broadening (Liang et al., 2010; Schmolesky et al., 2000; Leventhal et al., 2003), which was suggested as a potential mechanism behind dedifferentiation (J. Park et al., 2012). While age-related neural broadening was reported in animals using continuous, circular variables, these had not been investigated in human fMRI work. Due to the similarity in their approaches, both *article I* and *II*, addressed this disconnect. Their results correspond and together they provide compelling evidence for age-related ND in human fMRI even when stimuli are analogous to those used in the referenced animal research. This is reflected by age differences in classification accuracy as well as wider fMRI-level tuning functions in older adults. The lower classification accuracy found in older adults means that neural representations of individual directions are less distinguishable from those of the other directions. Both studies converge on this finding of decreased neural specificity in older age in the EVC.

When putting these results in the context of previous research, it is important to distinguish two different types of ND that have been investigated in human fMRI in the past: across- and within-category (see section 1.4). Across-category (or category-level) dedifferentiation describes changes in category-specific processing, for instance when areas involved in scene processing

respond more to other types of stimuli (D. C. Park et al., 2004; Carp, Park, Hebrank, et al., 2011; J. Park et al., 2012; Zebrowitz, Ward, Boshyan, Gutchess, & Hadjikhani, 2016; Zheng et al., 2018; Koen et al., 2019; Srokova, Hill, Koen, King, & Rugg, 2020). Within-category (or item-level) dedifferentiation, on the other hand, is used to reference changes in the specificity of neural responses to stimuli stemming from the same category (Goh et al., 2010; Yassa, Mattfeld, Stark, & Stark, 2011; St-Laurent et al., 2014; Reagh et al., 2018; Zheng et al., 2018). The works included in this thesis show evidence for within-category dedifferentiation. Previous investigations that applied within-category approaches have produced mixed results. This might be related to a number of factors. One of them is the methodological approach used. A number of studies that provided evidence in favor of within-category dedifferentiation with age (Goh et al., 2010; Yassa et al., 2011; Reagh et al., 2018) applied the method of repetition suppression (Grill-Spector, Henson, & Martin, 2006 and see Segaert, Weber, de Lange, Petersson, & Hagoort, 2013). In this approach, a loss in specificity is measured by the adaptation of neural responses to repeated presentations of the same stimuli, expressed in diminished activity. Since adaptations are stimulus-specific, stimuli that are perceived as new elicit non-adapted responses. Goh et al. (2010) repeatedly presented older and younger adults with pictures of faces and could show that older adults' adaptation extends to similar faces. This was interpreted as evidence for older adults' less differentiated responses to different faces. In contrast to these studies, research that applied MVPA (Haxby et al., 2001) could not provide strong evidence for within-category dedifferentiation (Zheng et al., 2018; St-Laurent et al., 2014). The approach applied in *article I* and *II* of this thesis was based on the classification of multivariate activity patterns. Both articles suggested within-category dedifferentiation, diverging from the idea that such findings are exclusive to the usage of repetition suppression.

Repetition suppression could, however, offer a valuable tool when investigating ND in the case of a continuous and circular variable. A study by Shine et al. (2016) showed the presence of repetition suppression in the case of participants changing allocentric facing directions in a virtual space. A strength of this approach is that it does not require the definition of individual categories or classes. Rather, changes in fMRI activation levels after adaption could be related to the magnitude of directional change. This would yield a detailed profile of specificity changes, possibly with higher resolution compared to the present investigations. One disadvantage would be that the systematic adaption towards specific direction requires imposed

navigation through space (for examples, see Shine et al., 2019). This presents a challenge in the context of free roaming through space, and therefore would have been a problem for the data analyzed in this thesis. Nonetheless, a higher resolution when investigating neural similarity changes, or potentially eliminating the need for binning overall, could warrant experiments using constrained navigation. In *article I* we showed that the reported Gaussian similarity structure also persisted for smaller bin sizes of 10° instead of 60°. An elimination of binning altogether would, however, be preferable and presents a valuable addition of the repetition suppression approach.

Another factor behind the mixed results of previous work regarding within-category dedifferentiation could be a quantified stimulus similarity. For instance, Goh et al. (2010) investigated similar and dissimilar face stimuli. Their results showed that evidence for age-related ND was only seen for similar faces, with no age difference for less similar faces. A study that also investigated face stimuli but without a distinction by similarity did report null results in visual areas (Zheng et al., 2018). One strength of the present work is that different walking directions cannot only be separated into more or less similar exemplars, but are distributed along a continuous similarity metric (i.e. angular distance). Therefore, the stimuli eliciting different neural responses are equidistant and span the entire possible stimulus space. The analyses of fMRI-level tuning functions in particular showed the importance of a quantifiable distance metric in the investigation of neural specificity. Taken together, this work's finding of age-related ND over the continuous variable of walking direction across articles *I* and *II* shows consistent results by applying a MVPA-based investigation of within-category dedifferentiation. How the specific application of a multivariate classifier or the usage of a quantifiable distance metric between stimuli contributed in this regard remains an open question.

Advantages of measuring fMRI-level tuning functions

The usage of stimuli connected by a quantifiable distance metric further allowed the extraction of ROI-specific fMRI-level tuning functions. These resulted from the analysis of the classifier's confusion matrix, specifically by relating the amount of classifier confusions between two directions to their angular distance. In doing so, the measure is separated from overall classification accuracy and presents an analysis of the *errors* made during classification (for more information on confusion matrices, see Powers, 2020). This was also reflected in the statistical

analysis, in which the peak of the tuning curves (corresponding to classification accuracy) were excluded from the model comparison of the tuning curves shape (Gaussian vs. Uniform). This independent assessment of fMRI-level tuning functions allowed me to investigate additional facets of age-related ND.

Specifically, it addressed not only *if* neural specificity changes with age but also *how* it changes. One main question in the context of age-related ND is whether changes in older adults' neural specificity are caused by a widened spectrum of a cell's (or population's) preferred stimuli (neural broadening) or rather the absence of preference (neural attenuation, see section 1.4). These potential mechanisms were derived from cell-specific animal work on tuning functions in aging (Schmolesky et al., 2000; Leventhal et al., 2003; Hua et al., 2006; Yu, Wang, Li, Zhou, & Leventhal, 2006; Y. Yang et al., 2008; Liang et al., 2010). Previous fMRI work on age-related ND in humans provided evidence for neural broadening (Hill, King, & Rugg, 2021), neural attenuation (Koen et al., 2019), or both (J. Park et al., 2012; Srokova et al., 2020). The results in favor of each process vary based on the investigated stimuli (e.g. scenes vs. faces) and brain area, suggesting that both mechanisms are involved in changes to neural specificity with age. These results were, however, largely based on category-based approaches. Investigating continuous encoding of direction allowed me to test the claims made by neural broadening and attenuation more directly. This presented an advantage of being able to measure fMRI-level tuning functions since classification accuracy alone is not able to distinguish between these processes. The analysis of the tuning function's shape showed that the similarity structure of direction representations in the EVC and RSC remains intact in older age. The neural similarity in both age groups decreases as a function of angular distance between the underlying directions, expressed by a Gaussian shape of the respective tuning functions. Further, *article I* and *II* showed that the Gaussian curves fitted to the EVC tuning functions of older adults were wider compared to younger adults. This finding is consistent with the idea of neural broadening. If the underlying populations would lose their stimulus preference (neural attenuation), this would likely be associated with a deterioration of the investigated similarity structure (i.e. a uniform rather than Gaussian distribution of classifier errors). However, the maintenance of the similarity structure (EVC and RSC) as well as wider fMRI-level tuning functions in the EVC speak in favor of neural broadening. Based on our approach these findings provide evidence for neural broadening in the context it has been reported in animal work.

Importantly, the assessment of fMRI-level tuning is not exclusive to the approach used in this study. It could therefore also help to further understand the mechanisms of across-category dedifferentiation. Using fMRI, the signals of neural populations have been investigated regarding their tuning to visual categories, including distinct features of faces (Zhang, Jiang, Song, Zhang, & He, 2021) or more general features of objects, like animation (Haxby et al., 2011). Investigating how these tuning profiles change over age might enable further understanding of the diverse results regarding the mechanisms behind category-level ND. The same is true for within-category approaches and other continuous variables besides direction. Importantly, measuring fMRI-level tuning for continuous variables does not necessarily require a circular variable. One example given by earlier work is the assessment of number tuning in the human intraparietal sulcus (Piazza, Izard, Pinel, Le Bihan, & Dehaene, 2004). Parietal and prefrontal cell populations in macaque monkeys have been found to code for numerical quantity on the basis of neurons exhibiting Gaussian tuning (Sawamura, Shima, & Tanji, 2002; Nieder & Miller, 2003, 2004). Piazza et al. (2004) showed similar tuning in humans using non-invasive fMRI. Spaces that are continuous but not circular are commonly encountered in daily life (e.g. auditory frequency) and investigating age-related changes in their tuning profiles would allow a broader perspective of ND, for instance towards domains other than vision. Additionally, it should be noted that the assessment of tuning has proven useful besides the investigation of ND. One study tested how tuning functions of populations representing the spatial position of a stimulus change when said stimuli are paired with an aversive outcome (Friedl & Keil, 2021). Using a similar model comparison approach as *article I* and *II* the authors showed that tuning functions do become more sharp once stimuli are associated with negative outcome. In summary, the assessment of fMRI-level tuning in this work has supported a closer link between animal work on neural broadening and its involvement in age-related ND in humans. The investigation of tuning profiles could furthermore provide an additional perspective on established findings in the literature of age-related ND and beyond.

Findings in the early visual cortex: which signal dedifferentiates?

The results presented in this thesis show consistent evidence for age-related ND in the EVC. These findings demonstrate age differences in the specificity of visual signals in response to varying travelled directions. Just as during natural navigation, direction and visual input were

linked when participants traversed the virtual arena in both *article I* and *II*. Distinguishing between different walking directions therefore can be perceived as a problem of distinguishing different scenes. However, there are various aspects of the visual input that set it apart from scene stimuli used in previous investigations of age-related ND (e.g., see Zheng et al., 2018; Koen et al., 2019). What participants saw during different walking directions corresponded to sectors of one continuous, 360° scene. Since walking direction events were independent of the navigator's position in the arena and allocated to bins of 60°, the scenic input was not identical, but varied within the same walking direction. Further, due to participants' movement in space, the visual input carried optic flow, an important characteristic in the estimation of heading direction (Warren, Morris, & Kalish, 1988) and distance travelled (Frenz, Bremmer, & Lappe, 2003). Therefore the findings in the EVC are describing the age-related dedifferentiation of neural patterns in response to complex visual input relevant for spatial navigation and orientation.

One important question is which mechanistic changes might cause this age-related loss of pattern distinctiveness as measured by fMRI. Given the findings in the EVC, changes in the specificity of visual processing are one likely candidate mechanism. The visual domain was also the focus of studies that led to the idea of neural broadening as a mechanism behind age-related ND. In particular, they reported wider tuning in several instances of direction and orientation selective cells in primates (Schmolesky et al., 2000; Leventhal et al., 2003; Y. Yang et al., 2008; Liang et al., 2010) and cats (Hua et al., 2006). These neurons pick up on the orientation of basic scenic features such as edges and light-dark contours (Hubel & Wiesel, 1968). The existence of neural populations that exhibit such orientation selectivity in the human EVC has been demonstrated using fMRI (Kamitani & Tong, 2005; Haynes & Rees, 2005; Yacoub, Harel, & Uğurbil, 2008). Although the results of this thesis hint towards the presence of wider tuning functions in older adults (neural broadening), there has not been any reports that age influences the tuning profiles of these selective populations in humans to date. Given the complexity of the scenic input, especially the presence of optic flow, the sources of decreased specificity of the measured activity patterns could furthermore lie in the neural basis of other visual processing systems. An additional promising site could be neurons selective to visual motion. Investigations of the primate visual cortex have shown that V1 contains cells responding to specific motion directions (Movshon, Adelson, Gizzi, &

Newsome, 1985; Maunsell & Newsome, 1987), a finding that has, on the population-level, also been demonstrated in humans (Helfrich, Becker, & Haarmeier, 2013). These cells, as well as targets of their downstream projections like MT, were found to be of relevance for the perception of optic flow and self-motion (Pasternak & Merigan, 1994; Salzman, Murasugi, Britten, & Newsome, 1992; Furlan & Smith, 2016; Cullen, 2011), both processes showing strong impairment with healthy as well as pathological aging (Lich & Bremmer, 2014; Kavcic, Vaughn, & Duffy, 2011; H. A. Allen, Hutchinson, Ledgeway, & Gayle, 2010; Chou et al., 2009; Lalonde-Parsi & Lamontagne, 2015). The results in the EVC could be caused by age-related changes in either, or both of these two well-tuned systems. Addressing this open issue would be a promising avenue for future research, to further understand the results presented in this thesis as well as the visual component involved in spatial navigation. One potential experiment in this regard could, for instance, use a procedure similar to the navigation-based approach in articles *I* and *II*, but with minimized features of the environment (e.g. see Kirschen, Kahana, Sekuler, & Burack, 2000). This could be used to manipulate the influence of optic flow or orientation of visual features on the measured neural activity. Further, one could apply the presented methods outside a navigation paradigm and directly investigate the neural specificity in response to basic visual features like rotating bars (see Leventhal et al., 2003).

Alternative explanations for the observed age differences in EVC pattern specificity include visual acuity. Rather than originating during the processing of visual input they could be the consequence of, for instance, more blurry vision in older adults. Given the designs of *article I* and *II*, it is not possible to entirely exclude this factor's contribution to the presented results. However, what argues against this interpretation is that both experiments only investigated participants with normal or corrected-to-normal vision, effectively reducing potential perceptual differences. In relation to this, investigations of the data set analyzed in *article I* showed no evidence for age differences in basic visual processing, measured by a contrast of cue-onset (see supplementary, Schuck et al., 2015). Furthermore, studies focusing on perceptual processes important for spatial navigation like the estimation of distances (Bian & Andersen, 2013; Norman et al., 2015) and surface slant (Norman, Crabtree, Bartholomew, & Ferrell, 2009) reported either no age differences or even better performance in an older age group. Besides differences in visual acuity, parts of my results could also be explained by altered behavior during perception such as eye movements. Specifically, a study by Dowiasch, Marx, Einhäuser,

and Bremmer (2015) demonstrated that older adults exhibit slower as well as a reduced number of saccades when visually perceiving real world environments during navigation. How precisely these factors might contribute to the reported results warrants further investigation. Ideally, these should include a detailed assessment of visual acuity and measurements of visual scene exploration, for instance through eye-tracking.

Findings in the retrosplenial cortex: could it be compensatory?

Besides the EVC, the RSC also showed above-baseline decoding of the current walking direction in *article I* and *II*. Interestingly however, signals in this ROI did not show any evidence for altered neural specificity between younger and older adults. These results are interesting with regard to two major questions. The first question is which signal is measured in the RSC. While the signal carries information about the current walking direction similar to the EVC, it did not show the same age-related dedifferentiation. This suggests that it is unlikely for the signals measured in the RSC to be a mere propagation of less specific visual signals. The RSC is a downstream area of visual processing and integrates visual input with other sources of information (Van Groen & Wyss, 2003). *Article I* investigated the influence of purely visual information on the decoding of walking direction from the EVC and RSC. While still highly responsive to the visual scene, across all participants its influence was weaker in the RSC compared to the EVC. This is in line with the idea that the RSC likely integrates additional sources of information in its walking direction signal. One option underlying this slightly decreased dependence on the visual scene could be that the signal measured in the RSC is more heavily influenced by HD cells. Studies in rodents have demonstrated populations of HD cells in the RSC (L. L. Chen, Lin, Green, et al., 1994; L. L. Chen, Lin, Barnes, & McNaughton, 1994; Cho & Sharp, 2001), while human work has shown that strokes affecting the RSC leave patients with an impaired sense of direction (Takahashi, Kawamura, Shiota, Kasahata, & Hirayama, 1997). These findings are accompanied by results from human fMRI showing allocentric direction coding in the RSC, similar to HD cells (Shine et al., 2016). The signal measured in the RSC could therefore be the result of an integration process of visual information on the one hand and allocentric signals of walking direction on the other. However, given the strong reciprocal connections with other areas, for instance the hippocampus and thalamus (van Groen, Vogt, & Wyss, 1993; Naber & Witter, 1998), it is likely that other

sources also contribute to a different type of direction signal compared to the EVC. The exact nature of these sources cannot be disentangled within this thesis. Nonetheless, our results speak in favor of differing signals of walking direction in the EVC and RSC.

This leads us to the second important question, namely the reason behind the missing evidence of age-related ND in the RSC in both *article I* and *II*. Potential explanations for this finding fall in either of two categories: either there is age-related ND, but we cannot measure it, or the effect is truly absent. Factors that could influence the measurement would likely be related to our methodological approach. For one, it could be that the number of directional bins for walking direction events used to train the classifier was too coarse. Decreasing the size of each bin and increasing the number of direction classes during classifier training and testing would help to reach a better resolution of the tuning curve. This would also increase the approach's sensitivity to detect smaller age differences. In turn, the experiment would require more data, which could either be achieved by guiding participants' navigation or increasing the time on task. Taking these measures would, however, not help in case the problem lies in the task. All virtual navigation had to be conducted during fMRI, while participants were lying on their back with instructions to not move. This eliminated any vestibular input during virtual navigation. Signals of HD cells are strongly dependent on vestibular information (Blair & Sharp, 1996; Stackman & Taube, 1997; Clark & Taube, 2012; Yoder & Taube, 2014). Especially when considering the integrative role of the RSC, missing motion cues of one's own body could affect its signal specificity. Older adults have been shown to exhibit losses in vestibular function (Rosenhall & Rubin, 1975; Lopez, Honrubia, & Baloh, 1997; for a review, see Anson & Jeka, 2016), a finding related to their decreased performance on spatial navigation tasks (Xie et al., 2017). In this case, it would be possible that higher RSC signal specificity in younger adults was hindered by the task procedure. Testing this explanation presents a challenge that could only be addressed using mobile neuroimaging in combination with high-end, head-mounted VR setups that allow researchers to track participants' location in space. Such methods have recently gained traction (Miyakoshi, Gehrke, Gramann, Makeig, & Iversen, 2021) and present a major opportunity in the investigation of human spatial navigation. How well these setups will be able to compensate for the reduced spatial resolution of electroencephalography (EEG) measures remains to be seen. The development of new technology such as portable magnetoencephalography (OPM-MEG, Tierney et al., 2019; Brookes et al., 2022), however, offers a

promising future solution to this problem.

Regarding the alternative explanation of the true absence of age-related specificity losses in the RSC, this thesis offers a highly speculative account. It could be that the computational processes in the RSC are subject to lifespan-related change and are altered in older age. This was suggested by age-differences found across *article I* and *II*. The results of a univariate fMRI analysis showed that activity in the RSC of older adults varied stronger between different directions compared to younger adults. This is combined with a finding in *article II*, demonstrating that L-DOPA had an influence on RSC signal specificity in younger adults, while in older adults it did not lead to any specificity changes. When jointly considering these two results, one interpretation could be that the patterns with which the RSC reflects the outside world might change in older age in a way that decouples them from DA-related processing. This decoupling might increase older adults' resistance to signal dedifferentiation in the RSC. The idea that the brain's functional organization can change over the lifespan and thereby supports compensatory processing has been laid out in further detail in the introduction (see section 1.3). The conclusion that the reported findings may be related to a similar compensatory process, however, requires a connection to a behavioral benefit. Our investigations could not provide evidence for such a benefit. In summary, considering the differences between the results reported in the RSC and early visual areas, it is unlikely that they present a pure propagation of visual input. Further, the reason for why there was no evidence for age-related ND in the RSC cannot be answered in a satisfying fashion by the work included in this thesis. The suggestions that the RSC exhibits a compensatory change of its functional organization remains highly speculative and lacks important evidence regarding its behavioral benefit. The investigation of this potential age-related change, however, presents an interesting target for future investigations.

Potential mechanisms of age-related neural dedifferentiation

One central goal of this dissertation was to further understand the mechanisms underlying age-related ND. In general, ND is based on two potential sources: sensory input or the neural processing of said sensory input. The sensory category includes processes that allow us to perceive the outside world free of systematic distortion. Above it has been mentioned how age-differences in visual acuity might influence results found in the EVC. Especially in the

context of spatial navigation, it has been proposed that changes in vestibular perception play a role in less specific neural signals (Stangl et al., 2020). Due to the missing vestibular input caused by the fMRI-based approach and the missing assessment of visual acuity after correction, the contribution of such sensory sources towards the findings reported in the included works cannot be accurately quantified. Longitudinal studies have shown that rates of change in cognitive measures and rates of change in visual acuity in aging are related and might share a common factor (Lindenberger & Ghisletta, 2009). Cognitive abilities like memory and fluid processing are evidently related to neural signal specificity (St-Laurent et al., 2014; St-Laurent & Buchsbaum, 2019; Zheng et al., 2018; Koen et al., 2019; D. Park, 2010). For a more principled understanding of ND and how it might be involved in shared rates of age-related change, the contribution of sensory sources will need to be defined in future research.

Besides sensory differences in aging, decreased signal specificity can also stem from neural processing of sensory input. In particular, *article II* was dedicated towards this endeavor and allowed the investigation of a causal role of DA in neural signal specificity, as predicted by computational models (Li et al., 2001). The reported findings speak in favor of a causal role of DA in the specificity of neural representations of walking direction. Specifically, the administration of the DA precursor L-DOPA enhanced the measured signal specificity across both age groups. While this was a general finding across the investigated ROIs, exploratory follow-up analyses suggested that the RSC and the hippocampus profited strongest from higher availability of DA. This is in line with the computational models of signal specificity (Li et al., 2001) that based their predictions on DA's effect on neural gain (Cohen & Servan-Schreiber, 1992; Thurley, Senn, & Lüscher, 2008). This study is not the first to show this causal influence of DA on signal specificity measured in human fMRI. Another study by Abdulrahman, Fletcher, Bullmore, and Morcom (2017) showed that the administration of a DA agonist (Bromocriptine) and antagonist (Sulpiride) causally influenced ND of categorical memory contents in the hippocampus. *Article II* supports this relationship in the context of the continuous space of walking direction. Importantly, this suggests that a similar DA-based mechanism applies for across- as well as within-category dedifferentiation, in particular content that is connected by a continuous similarity metric. One factor that warrants further investigation regarding *article II* is the absence of overall age differences in the effect of L-DOPA on signal specificity. Only within the RSC was there an evident difference between age groups expressed in the absence

of specificity enhancing effects of L-DOPA in older adults. As mentioned above, a highly speculative account for this finding could be an age-related change in the computational role of the RSC in the investigated task. Otherwise, the findings seem to deviate from the established inverted-U-shape relationship between cognitive performance and levels of DA (Cools & D'Esposito, 2011; Vijayraghavan, Wang, Birnbaum, Williams, & Arnsten, 2007). Whether this is an effect of the applied task or a general finding in the context of continuous variables will need to be determined in future studies.

Besides the availability of DA, there are also other potential sources of age-related dedifferentiation that might be related to neural processing. For instance, we found that DA did not influence signal specificity in EVC, the area we found consistent evidence for age-related neural dedifferentiation. This finding is in line with the relatively low density of DA receptors in the visual cortex (Lidow, Goldman-Rakic, Rakic, & Innis, 1989). Another mechanism that might show stronger influence on dedifferentiation in the visual cortex is GABA-related inhibitory processing. The administration of GABA agonists in senescent monkeys has been shown to restore tuning specificity of orientation selective cells in V1 (Leventhal et al., 2003). Establishing a link between age-related ND in the EVC and levels of GABA would allow conclusions about the nature of the findings in the EVC and if they are indeed a consequence of less specific tuning of orientation selective cells. A link between GABA and neural specificity has already been established by previous research. Based on the findings of Leventhal et al. (2003), one study investigated the relationship between levels of GABA and age-related, across-category ND in the ventral visual cortex (faces vs. houses, Chamberlain et al., 2021). Older adults exhibited both reduced GABA levels and decreased neural distinctiveness in visual processing. Furthermore, these two measures were linked in older adults, suggesting a connection between decreasing GABA and lower neural specificity across distinct visual categories. A similar role of GABA has been shown in the context of age-related ND in the auditory cortex, when processing either foreign speech or music (Lalwani et al., 2019). The investigation of a continuous variable in this context would also be of value due to its closer link to the findings by Leventhal et al. (2003). GABA also presents a connecting factor between age-related ND and another potential mechanism. The fMRI signals measured in older adults have been shown to exhibit lower variability (Nomi, Bolt, Ezie, Uddin, & Heller, 2017; Garrett, Lindenberger, Hoge, & Gauthier, 2017; Grady & Garrett, 2018; for a review, see Grady & Garrett, 2014). Less vari-

ance in the neural signal could be a contributing factor towards less precise representations. Interestingly, the administration of GABA can restore older adults' signal variability to levels present in younger adults (Lalwani, Garrett, & Polk, 2021), presumably because an optimal balance between inhibition and excitation allows networks to act in a flexible manner (Poil, Hardstone, Mansvelder, & Linkenkaer-Hansen, 2012; Agrawal et al., 2018). The connection between GABA, neural signal variability, and neural specificity are yet to be addressed directly. Therefore, besides DA, a more detailed investigation of GABA will also contribute to a more principled understanding of ND and its mechanisms.

In summary, *article II* further investigated the findings of *article I* and provided additional evidence in favor of a causal link between levels of DA and the specificity of neural representations, a prediction based on computational models (Li et al., 2001). It showed that neural representations reflecting a continuous space exhibit increased specificity under higher availability of DA. Identifying the reason behind differing effects of L-DOPA between the investigated age groups and ROI will require additional studies. Moreover, the relationship between GABA, fMRI signal variability, and neural specificity should be characterized in more detail. This will help to build a thorough understanding of the mechanisms that underpin age-related ND.

Aging and abstract continuous space

With *article III* this thesis aimed to move away from spatial cognition and applied an outcome-based learning task to investigate if aging also influences the representation of more abstract (non-spatial) continuity. The reported results included that surprising outcomes eliciting large prediction errors (PEs, a scalar variable) influenced the behavior of older adults more strongly relative to younger adults. What does this finding tell us about the question how aging shapes representations of continuous space? Compared to articles *I* and *II*, this behavioral finding does not speak towards altered *neural* representations of continuous space in older age. Rather, it compares age groups regarding how different sections of the continuous space of PEs are represented in the decision making process. Choices following surprising events as well as participants' outcome estimates suggest that, in older adults, higher PEs at the extreme of the spanned space are over-represented compared to younger adults and more readily influence learning and decisions (for accounts towards uncertainty, see *article III*). In turn, the representation of the continuous space of PEs in choices made during a RL task seems to be shaped by

age.

Why might this pattern of over-weighting appear in older adults? One idea might be that it is a consequence of reaching the limits of finite cognitive resources. Also outside of the aging literature, the over-weighting of extremes has been reported in several contexts, such as memory recall (Madan et al., 2014), when calculating the mean of samples (Spitzer, Waschke, & Summerfield, 2017), or estimation of an event's probability (Lichtenstein, Slovic, Fischhoff, Layman, & Combs, 1978). Recent accounts have proposed that this pattern reflects the rational and efficient use of finite resources (for a review, see Lieder et al., 2018). What has indeed been shown in sequential sampling tasks is that the over-weighting of extremes specifically arose in the context of increased processing demands (Spitzer et al., 2017; von Clarenau, Pachur, & Spitzer, 2022). Considering that older adults are more challenged by decision-making tasks in comparison to younger adults (Tymula et al., 2013), one explanation of their over-representation of surprising events in *article III* could lie in increased cognitive load. However, although this factor might contribute to the behavioral patterns at hand it does not capture the wide variability in older adults behavior in this context. By applying monetary lotteries, Pachur et al. (2017) found a preference of older adults for more risky options offering higher monetary gains, a pattern that was independent of cognitive ability. The same study also showed that age-differences in risk aversion varied depending on the domain in question, for instance, if participants instead gambled for a loss. A comprehensive understanding of why age might introduce patterns of over-representation therefore requires an integration of findings across different tasks and contexts, a challenge future research should aim to address.

Another important question is which characteristics define the altered representation of large PEs in choices of older adults. Precisely how much more influence do they have? Does an over-representation scale with the encountered magnitude of the PE or does it rather follow a dichotomization into surprising and non-surprising events? *Article III* attempted to capture this specific relationship in its computational models, specifically by allowing the *Surprise* model to reflect various potential relationships between PE magnitude and learning rate. In turn, the model could display patterns of under-, over-, and similar weighting of surprising events, relationships expressed in the models parameters. Although the Surprise model overall offered the best account of participant's choices relative to other candidate models, comparing younger and older adults' parameter values did not reflect the age differences evident in behavior. In

this, it did not allow conclusions in how aging might influence the precise mapping between the continuous variable of PEs and their representation in learning and choice. What might have caused this mismatch of model parameters and behavioral results could be an inherent challenge when investigating surprising events in a stationary environment, namely that such events can only appear in low frequency. In turn, trials in which participants' behavior reflects the impact of surprising outcomes only represent a small proportion of the trials used to fit computational models, making it more difficult to accurately mimic the process at hand. While this could be addressed by increasing the amount of bandits in the task, this was avoided to keep the complexity of the task at a manageable level. The reduced control over the experimental environment during online data collection has been shown to lead to increased noise (Crump, McDonnell, & Gureckis, 2013), a finding that should be even more carefully considered in a study including different age groups (for additional thoughts on the group of older adults sampled in online data collection, see *article III*). However, it should be noted that participants' overall performance in the task suggested that more complex tasks are likely feasible. Defining the characteristics of the altered representation of large PEs in older adults' choices should be a goal of additional studies, preferably a combination of online- and in-lab approaches. A better understanding of the exact nature of the behavioral changes could allow to relate the presented findings in the context of more abstract continuous space to changes in the spatial domain and potentially investigate their relationship with neural dedifferentiation.

4.2 Limitations

Since *article I* and *II* aimed to address related questions and share a similar methodology, this section on the overarching limitations of this thesis will focus on these two publications. The limitations of *article III* apply and are addressed in the respective discussion section (see appendix E).

Unclear relationship to behavior

In order to judge the relevance of ND for age differences in spatial memory, it is necessary to look at its relationship with behavior. The results across both studies were consistent in that they showed relationships between neural specificity and task performance. However, these

relationships involved different ROIs across studies. *Article I* found a relationship between increased spatial memory performance and higher decoding accuracy of walking direction in the RSC independent of age. In *article II*, task performance was related to decoding accuracy in the EVC but only in younger adults. Individually, both findings can be interpreted in line with previous research. Moffat, Elkins, and Resnick (2006) demonstrated that the RSC plays a role during online navigation and is subject to age-related changes in its activation during this process. Further, they reported that activity in the RSC was related to task performance. Regarding the relationship in the EVC, vision is known to be important for stable directional signals and path integration (Goodridge, 1998; Jeffery, 2007). It is therefore conceivable that less precise visual signals could influence navigation performance. Nonetheless, the relationships between measures of ND and behavior varied substantially between both works and elude a consistent interpretation. Another limitation in this regard is that the investigated behavioral measure did not allow a clear separation between navigation ability and spatial memory performance. Task performance was assessed by the euclidean distance between the true location of an object and the participant's placement. It is not possible to disentangle if this distance was due to inaccurate memory or rather inaccurate navigation towards a desired location. This limitation could be addressed by investigating other behavioral measures. One option would be to additionally measure navigation efficiency. This could be quantified as the length of a travelled path from a starting position to a desired goal location. Additional work should therefore focus on further characterizing the inconsistent relationship between ND of walking direction signals and spatial navigation. To achieve this it would be valuable to include multiple behavioral measures and assess separate relationships towards spatial memory and navigation ability.

Data acquisition using a virtual environment

The collection of fMRI data imposes limitations, especially when investigating a process like spatial navigation that extensively relies on body-based cues (X. Chen, McNamara, Kelly, & Wolbers, 2017; Stangl et al., 2020). The absence of vestibular input in particular has negative consequences for the navigation performance of humans in real-world (Glasauer, Amorim, Viaud-Delmon, & Berthoz, 2002) as well as virtual settings (Brandt et al., 2005). Similar results have been presented for other stimulation that is absent while undergoing fMRI, such

as active motion (Wang & Simons, 1999; Witmer & Kline, 1998). The differences between virtual and real-world navigation have been discussed thoroughly elsewhere (see Taube, Valerio, & Yoder, 2013). These differences could also be relevant for the measurement process and subsequent conclusions. A good example is the absence of above-baseline decoding of walking direction in the subiculum and thalamus reported in *article I*, which might be linked to missing vestibular input. Both areas strongly rely on vestibular information to generate direction signals (Stackman & Taube, 1997; Stackman, Clark, & Taube, 2002). It remains open if this circumstance might interact with age and potentially influences older adults more than younger adults. While it has been shown that the use of VR methods is feasible with older adults with and without AD (R. Davis, 2021), it can still pose a major challenge for older adults (for a review, see Diersch & Wolbers, 2019). Common difficulties for older adults when confronted with VR are cybersickness (Liu, 2014) and less experience with new technology (Barnard, Bradley, Hodgson, & Lloyd, 2013). The results presented in *article I* and *II* might therefore be influenced by selection effects. However, participants were trained in the use of the dektop VR setup prior to the experiment. Together with the finding that cybersickness does not seem to be a phenomenon exclusive to the older age group (Saredakis et al., 2020), it seems unlikely these factors might account entirely for the observed age differences in signal specificity.

Pre-defined ROIs and findings in the motor cortex

Both neuroimaging studies applied an ROI-based approach. The choices for which ROIs to be included in the analysis was built upon previous findings related to (head-)direction signals (subiculum, thalamus, entorhinal cortex, hippocampus, and RSC; Winter & Taube, 2014; Munn & Giocomo, 2020; Leutgeb, Ragozzino, & Mizumori, 2000; Ben-Yishay et al., 2021; Shine et al., 2016, 2019). Additional ROIs were chosen to analyse primarily visual signals (EVC) and to provide a motor control (M1). The ROI-based approach does not allow any claims about other regions, neither if they may contain decodable information about the current walking direction nor age differences therein. In a more data-driven approach, the same analysis could be carried out using a searchlight procedure (Kriegeskorte, Goebel, & Bandettini, 2006). However, considering that both approaches have their pitfalls, previous investigations have suggested combining them (Etzel, Zacks, & Braver, 2013). This could be a valuable avenue to

pursue for future investigations.

A surprising finding of this work included the anticipated control region. I chose M1 as a control ROI because the forward-tilt motion of the joystick required to move forward in the virtual environment was identical for all directions. Unexpectedly, the analysis found moderate decoding accuracy of walking direction in the M1, specifically in *article II*. The lack of a clear control region that was defined a-priori therefore presents a limitation of the included works. The background of the decoding performance in M1 can only be speculated upon given the present data. A previous fMRI study showed that visual aspects of directed motor movements were coded in M1, under the premise that they are coupled with consequential motoric responses (Eisenberg, Shmuelof, Vaadia, & Zohary, 2011). Given that this was the case in our task, these findings present a potential source of the observed direction information in M1. Another explanation could be that the classifier picked up on direction-dependent head motion during data acquisition which lead to an inflated chance-baseline. This effect was, however, addressed by including an indicator of head motion (framewise displacement) as a nuisance variable in the statistical models. What further speaks against an inflated chance-baseline as the reason behind the finding in M1 are clear null-results in other regions. What further separates the M1 results from those in the RSC and hippocampus is their independence of L-DOPA administration, although D_1- and D_2-receptor concentrations are higher compared to the occipital cortex (Lidow et al., 1989). Given their unexpected nature and deviation from other presented results, the decodability of walking direction in the motor cortex warrants further investigation. It furthermore underlines the large network that is supporting spatial navigation processes and the related challenge to identify a clear control region.

Analysis of unconstrained navigation

Regarding the methodological approach used in *article I* and *II*, the analysis of free navigation data presents an advantage. It enables the application of the introduced method of walking direction decoding in a large pool of data sets that included free navigation (e.g., see Doeller & Burgess, 2008; Doeller, Barry, & Burgess, 2010; Thurm et al., 2016; Kunz et al., 2015; Schuck et al., 2013). In this regard, it holds great potential to obtain and compare results across multiple studies and contexts. However, the missing control over the participants' paths during data acquisition also entails limitations that concern the assessment of fMRI-level tuning functions.

The free movement of participants leads to a non-random transition structure between directions (see *article I*, supplementary material). This is because turns to neighboring directions are more likely to occur than turns to, for instance, the opposite direction. What follows from this transition structure is that events of walking direction will be closer in time for neighboring directions. The relatively slow hemodynamic response function (HRF) could cause activity patterns of certain walking direction to contain lingering signal of the previous event. This could artificially increase neural similarity between neighbouring directions. To which degree this potential confound might contribute to the observed results is only possible to quantify in a task that involves a controlled transition structure between walking directions (e.g., see Shine et al., 2019). However, *article I* and *II* reported either no change to fMRI-level tuning functions in the older age group (RSC and hippocampus) or their widening (EVC). Interestingly, these findings seem to point in the opposite direction of the reported age-related changes in the blood-oxygen-level-dependent (BOLD) signal would suggest in this context: younger adults have been shown to exhibit higher auto-correlation of the BOLD signal (Geerligs, Tsvetanov, Cam-CAN, & Henson, 2017) which would be expected to increase the lingering signal and, in turn, lead to elevated confusions of neighbouring directions. If the findings are solely based on lingering signal, this would result in wider tuning functions in younger compared to older adults. In line with this, investigations of the HRF have shown that there are no changes in its duration between age groups (West et al., 2019) which could have a similar effect as differences in auto-correlation. Additionally, analyses of the time between events in *article I* (see supplementary material) showed that older adults exhibit longer delays between individual events, which contradicts the idea of wider tuning due to increased auto-correlation in the signal. This limitation should nonetheless be addressed by applying the approach on navigation data with a controlled transition structure. Finally, it should be noted that this point is exclusive to the investigation of fMRI-level tuning functions and does not affect classification accuracy, another reported measure of neural specificity.

Future research: a broader perspective

Starting from a more narrow point of view, there is one main goal future research should pursue to understand the findings presented in this thesis. This is to further characterize the physiological background of decreased specificity in walking direction signals in older adults'

EVC measured by our approach. Our assessments provide a closer connection to the potential mechanism of neural broadening found in monkeys (Schmolesky et al., 2000) compared to other investigations of ND. Nonetheless, whether some key characteristics of the animal findings will translate into our measure remains an open question. One very important factor is the manipulative power of GABA administration on the tuning specificity of V1 cells found by Leventhal et al. (2003). To see if the presented measure of neural specificity in EVC shares this susceptibility to levels of GABA, it would be valuable to repeat the included works while measuring or manipulating GABA levels in the occipital cortex. Another way to understand the physiological background in more detail would be with animal work directly. In animals, VR has been paired with invasive neuroimaging techniques like optical imaging (e.g., see Aronov & Tank, 2014; Huang et al., 2020). In this setup, age effects on the occipital signals could be analyzed in a similar fashion to the presented studies but with higher spatial and temporal resolution. Both of these avenues help to narrow down whether the results found in the EVC are indeed based on neural broadening of orientation selective cells in V1.

When widening our perspective, another future avenue could be the connection between the presented findings and other spatial signals. For instance, models of grid cell activity have assigned a major role to directional signals (for a review, see Raudies, Hinman, & Hasselmo, 2016). Interestingly, these models often consider movement direction instead of pure head direction due to the importance of velocity information for accurate grid cell firing (Raudies, Brandon, Chapman, & Hasselmo, 2015). Staying with the idea of animal VR, another useful application with regard to our findings could therefore be to assess the influence of specificity changes on grid cell firing. Moreover, grid-like coding has been identified in humans using fMRI (Doeller et al., 2010) and shows reductions in older age (Stangl et al., 2018) as well as adults carrying risk factors for AD (Kunz et al., 2015). Given the estimation of signal specificity of different walking directions and grid-like coding are both possible in the context of free navigation, it would be interesting to formally assess the relationship between both quantities in humans. The animal as well as human perspective could help to further understand the aging navigational system and see if ND might be involved as one of the potential mechanisms of its decline.

When broadening the view in the context of aging, it is important to not only consider trajectories of healthy aging, but also of pathological aging. The specificity of neural rep-

resentations has been shown to be associated with memory performance and other cognitive abilities (D. Park, 2010; Koen et al., 2019; St-Laurent et al., 2014; Zheng et al., 2018). Yet, there has so far not been any assessment of the role of neural specificity in memory pathology, for instance in the presence of mild cognitive impairment (MCI), AD, or adults with respective genetic risk factors. This gap should be closed by future research. This will enable greater understanding about the potential characteristics of pathological aging trajectories and possibly establish additional criteria to diagnose them in their early stages. Previous studies have found that spatial abilities might provide an early window into the diagnosis of neuropathology, specifically when having to differentiate types of dementia (Coughlan et al., 2018). Considering the strong influence of vision on spatial skills like path integration (Jeffery, 2007), it would be helpful to assess how less specific visual signals of walking direction might contribute in this regard. This might provide a more detailed profile of early AD diagnostics. Data sets that involve free virtual navigation while undergoing fMRI exist in risk carriers for AD (see Kunz et al., 2015). Analyzing them with the approach presented in this thesis might lead to the first conclusions in this matter. With this said, data from patients and risk groups can pose additional challenges, including limited amounts of data. Whether these limitations can be overcome will be determined by future work.

Taking a very wide perspective and moving towards speculation, when some of the questions above have been addressed, the findings could inform measures to aid older adults in real-world navigation. People suffering from dementia in particular are under increased risk of getting lost or disoriented in their daily life (Chiu et al., 2004; Emrich-Mills, Puthusseryppady, & Hornberger, 2021), often with dire consequences for their health (Woolford, Weller, & Ibrahim, 2017). Once the contribution of ND towards declining spatial abilities has been defined, with respect to visual direction signals in particular, the resulting insights could be translated into measures to potentially prevent disorientation. As an example, this could influence the design of large open spaces to decrease the confusability of different directions. This could be achieved by offering appropriate environmental cues clearly indicating the current travelling direction. An intervention to shape public spaces in a way that also properly accommodates the elderly should of course not wait until this work is completed. However, such an intervention might be improved by a thorough understanding of where errors in navigation are coming from and how they might be prevented.

As a final avenue of future research, I want to highlight the importance of a longitudinal assessment. While cross-sectional approaches are useful to identify potential age-related effects, they have been subject to strong criticism regarding their accurate estimation (Hofer & Sliwinski, 2001). That cross-sectional and longitudinal results in the research of age-related change can diverge profoundly has been demonstrated regarding older age (Nyberg et al., 2010) as well as in early life (Keresztes et al., 2022). In the field of age-related ND, only one study has so far provided longitudinal evidence (Chong et al., 2019). In the context of spatial navigation, longitudinal assessments have recently gained more traction especially regarding the early identification of pathological trajectories in aging (for a review, see Coughlan et al., 2018). Nonetheless, the number of such studies is low (Verghese, Lipton, & Ayers, 2017; Levine, Roe, Babulal, Fagan, & Head, 2022), especially those including structural (Lövdén et al., 2012; Korthauer et al., 2016; Daugherty & Raz, 2017) or functional neuroimaging (Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch, 2012). Unfortunately, so far no longitudinal approach has combined free virtual navigation and fMRI. This would allow researchers to assess within-participant changes in neural specificity over a continuous variable and, in turn, a less confounded perspective. A longitudinal assessment should therefore be a priority of future research. The flexibility of the presented approach might prove useful in this regard.

Conclusion

This thesis was conducted with the goal of understanding how aging shapes neural representations of continuous space. What led to this question was the finding that aging changes the specificity of neural signals responding to distinct visual categories. While neural broadening was suggested as a potential mechanism behind this process of age-related neural dedifferentiation, the studies that investigated neural broadening did so in neurons responding to a continuous variable rather than distinct categories. It was therefore important to address this gap and assess whether changes in neural specificity also occur in older adults' responses to continuous space. *Article I* utilized a spatial memory task involving free navigation in a virtual environment and found that neural representations of the continuous space of walking direction become less precise with age. *Article II* extended these results and provided evidence that, as suggested by computational models, dopamine plays a causal role in the dedifferentiation of neural signals, specifically within the context of continuous space. When we ask how aging

shapes neural representations of continuous spaces we can answer that it seems to render them less precise, similar to the findings in distinct categories. Furthermore, we can say that this process is at least partly influenced by dopamine functioning and the transmitter's modulatory role in the specificity of neural responses. Finally, *article III* investigated if aging also influences behavioral representations of learning from the more abstract continuous space of reward. Behavioral results suggested that large prediction errors located closer to the extremes of such a space are encorporated differently in the learning and decision process of older adults. To summarize, this thesis combined three empirical articles to provide additional insights into age-related functional changes in the human brain and behavior. By utilizing a newly developed approach, the presented work showed that the well-established finding of neural dedifferentiation in older age extends towards continuous space and is causally influenced by levels of the neuromodulator dopamine. These findings contribute to a more detailed understanding of age-related changes in memory functioning and spatial abilities and, therefore, might hold the potential of aiding with the diagnosis of pathological aging trajectories. Furthermore, the presented results speak in favor of the idea that age differences found in the representation of continuous spaces might also extend to more abstract domains.

At the beginning of this thesis, I mentioned that the aging brain does not have a good reputation and that it is often seen as subject to consistent and inevitable decline. In particular, in the context of age-related functional changes, I laid out that the brain's remarkable capacity to deal with losses in older age is often overlooked. It is intriguing to think that neural dedifferentiation might be part of the aging brain's toolkit to deal with neural compromise and allows older adults to avert more dire consequences for the affected cognitive functions. Rather than presenting a process of deterioration itself, dedifferentiation might be one of the brain's ways of *handling* deterioration, while at the same time maintaining functionality at an acceptable level. Finding out whether this is indeed the case, in my opinion presents the most important avenue of future research on age-related neural dedifferentiation. This thesis contributes towards this endeavour and hopefully makes clear to the reader that the aging brain's "bad reputation" is one thing above all: undeserved.

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Appendices

A Declaration of own share

Declaration pursuant to Sec. 7 (3), fourth sentence, of the Doctoral Study Regulations regarding my own share of the submitted scientific or scholarly work that has been published or is intended for publication within the scope of my publication-based work.

I. *Last name, first name:* Koch, Christoph
Institute: Max Planck Institute for Human Development, Berlin
Doctoral study subject: Psychology
Title: How aging shapes neural representations of continuous spaces

II. Numbered listing of works submitted (title, authors, where and when published and/or submitted):

1. Koch, C., Li, S.-C., Polk, T.A., & Schuck, N.W. (2020). Effects of aging on encoding of walking direction in the human brain. *Neuropsychologia*, *141*, 107379. doi: 10.1016/j.neuropsychologia.2020.107379
2. Koch, C., Baeuchl, C., Glöckner, F., Riedel, P., Petzold, J., Smolka, M.N., Li, S.-C., & Schuck, N.W. (2022). L-DOPA enhances neural direction signals in younger and older adults. *NeuroImage*, *264*, 119670. doi: 10.1016/j.neuroimage.2022.119670
3. Koch, C., Zika, O., & Schuck, N.W. (2022). Influence of surprise on reinforcement learning in younger and older adults. *PsyArXiv*. doi: 10.31234/osf.io/unx5y

III. Explanation of own share of these works:
The own share is assessed on the scale: *all – the vast majority – most – part*

Regarding II. 1.: development of concept (most), data pre-processing (all), data analysis (all), method development (most), discussion of results (vast majority), writing manuscript (vast majority), publication of code (all).

Regarding II. 2.: data pre-processing (vast majority), data analysis (all), method development (most), discussion of results (vast majority), writing manuscript (vast majority), publication of code (all).

Regarding II. 3.: Study conceptualization and design (vast majority), programming of task (all), data collection (all), data analysis (vast majority), writing manuscript (most), publication of code (all).

IV. Names and e-mail addresses for the relevant co-authors:

Regarding II. 1.: Shu-Chen Li (shu-chen.li@tu-dresden.de), Thad A. Polk (tpolk@umich.edu), Nicolas W. Schuck (schuck@mpib-berlin.mpg.de)

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Regarding II. 3.: Ondrej Zika (zika@mpib-berlin.mpg.de), Nicolas W. Schuck (see above)

05.12.2022, Christoph Koch

B Declaration of independent work

I hereby declare that:

- I completed this doctoral thesis independently. Except where otherwise stated, I confirm that the work presented in this thesis is my own.
- Where information has been derived from other sources, I confirm that this has been indicated in the thesis.
- I have not applied for a doctoral degree elsewhere and do not have a corresponding doctoral degree.
- I have acknowledged the Doctoral Degree Regulations which underlie the procedure of the Department of Education and Psychology of Freie Universität Berlin, as amended on August 8th 2016.
- The principles of Freie Universität Berlin for ensuring good academic practice have been complied with.

Christoph Koch

Berlin, 05.12.2022

C Article I

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D Article II

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L-DOPA enhances neural direction signals in younger and older adults

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ABSTRACT

Previous studies indicate a role of dopamine in spatial navigation. Although neural representations of direction are an important aspect of spatial cognition, it is not well understood whether dopamine directly affects these representations, or only impacts other aspects of spatial brain function. Moreover, both dopamine and spatial cognition decline sharply during age, raising the question which effect dopamine has on directional signals in the brain of older adults. To investigate these questions, we used a double-blind cross-over L-DOPA/Placebo intervention design in which 43 younger and 37 older adults navigated in a virtual spatial environment while undergoing functional magnetic resonance imaging (fMRI). We studied the effect of L-DOPA, a dopamine precursor, on fMRI activation patterns that encode spatial walking directions that have previously been shown to lose specificity with age. This was done in predefined regions of interest, including the early visual cortex, retrosplenial cortex, and hippocampus. Classification of brain activation patterns associated with different walking directions was improved across all regions following L-DOPA administration, suggesting that dopamine broadly enhances neural representations of direction. No evidence for differences between regions was found. In the hippocampus these results were found in both age groups, while in the retrosplenial cortex they were only observed in younger adults. Taken together, our study provides evidence for a link between dopamine and the specificity of neural responses during spatial navigation.

Significance Statement: The sense of direction is an important aspect of spatial navigation, and neural representations of direction can be found throughout a large network of space-related brain regions. But what influences how well these representations track someone's true direction? Using a double-blind cross-over L-DOPA/Placebo intervention design, we find causal evidence that the neurotransmitter dopamine impacts the fidelity of direction selective neural representations in the human hippocampus and retrosplenial cortex. Interestingly, the effect of L-DOPA was either equally present or even smaller in older adults, despite the well-known age related decline of dopamine. These results provide novel insights into how dopamine shapes the neural representations that underlie spatial navigation.

1. Introduction

A role of dopamine (DA) in spatial navigation is well established. Anatomically, spatial cognition depends on a network of brain regions centered around the hippocampus (HC) and retrosplenial cortex (RSC) (Burgess et al., 2002; Chersi and Burgess, 2015), both of which are targets of dopaminergic innervation (Berger et al., 1985; McNamara and Dupret, 2017). Behaviorally, spatial navigation abilities are influenced by DA functioning in younger as well as older animals and humans (Elghundi et al., 1999; Granado et al., 2008; Kentros et al., 2004; Thurm et al., 2016).

Much less is known about how DA might change the neural representations that support spatial navigation. Particularly interesting for human neuroscience are direction selective representations (Taube, 2007), which have been found, amongst others, in the HC, the RSC and visual cortex (Cacucci et al., 2004; Flossmann and Rochefort, 2021; Guitchounts et al., 2020; Shine et al., 2016), and can be decoded from human fMRI signals (Koch et al., 2020). We hypothesized that DA af-

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fects direction encoding in the human brain and tested this idea using a double-blind placebo controlled intervention design. Specifically, we predicted that oral administration of L-DOPA, a dopamine precursor, would influence how accurately walking direction can be decoded from multi-voxel fMRI patterns in the above named ROIs.

Next to its role in spatial navigation, DA has also received much attention in the context of aging, where reduced DA functions are prevalent and are thought to underlie age-related cognitive declines (Bäckman et al., 2006; Chowdhury et al., 2013; Li et al., 2010; Volkow et al., 1998). Computational models have shown that declining neuromodulatory effects of DA lead to losses in the signal-to-noise ratio of neural responses (Cohen and Servan-Schreiber, 1992; Servan-Schreiber et al., 1990), which in the aging brain can lead to neural representations that are less specific or "dedifferentiated" (Li et al., 2001; Li and Rieckmann, 2014). In line with these models, dedifferentiation has repeatedly been observed in older adults (OA) at the behavioral and neural levels (Carp et al., 2011a,b; Koch et al., 2020; Li et al., 2004; Park et al., 2004). Neural dedifferentiation, in turn, has been linked to decreased memory performance (Koen et al., 2019; Sommer et al., 2019; St-Laurent et al., 2014), establishing an explanatory link between DA, neural representations and cognitive aging.

These roles of DA in spatial navigation and aging might contribute to the pronounced decline in spatial cognition with age (Lester et al., 2017; Moffat, 2009; Schuck et al., 2015; Wolbers et al., 2014), and to the neural dedifferentiation of direction-selective (Koch et al., 2020) and hippocampal signals (Schuck et al., 2015) in the aging brain. Moreover, since the sharp decline of DA with age should lead to lower baseline availability of DA in OA, the effects of DA might be stronger in OA relative to younger adults (YA) – reflecting DA's inverted-U-shape relation to cognitive performance (Cools and D'Esposito, 2011; Li et al., 2010; 2013; Vijayraghavan et al., 2007). Indeed, one previous study found age-related effects of the DA receptor agonist bromocriptine on dedifferentiation in the HC (Abdulrahman et al., 2017). Moreover, HC-dependent episodic memory, spatial navigation, and learning have been found to be affected by genetic polymorphisms related to dopamine D2 receptor availability (COMT Val158Met, C957T CC; Li et al., 2013; Papenberg et al., 2014) or hippocampal function (KIBRA SNP rs17070145; Schuck et al., 2013; Schuck et al., 2018) in OA, but not YA. Based on these findings, we therefore also tested whether L-DOPA effects on walking direction decoding would be stronger in OA relative to YA.

Finally, we expected that DA could also influence the shape of population-based tuning functions of direction. Although direction-sensitive cells often have a preferred direction, they also fire in response to non-preferred directions in proportion to their similarity to the preferred direction (Taube, 2007). Hence, encoding of direction information seems to follow a Gaussian tuning function, in particular on a population level (Averbeck et al., 2006). Research has also shown that age-related neural dedifferentiation results in increased width of such tuning functions with age (Leventhal et al., 2003; Liang et al., 2010; Schmolesky et al., 2000), which we too have reported previously using fMRI (Koch et al., 2020). We therefore also investigated whether L-DOPA has effects on the precision of fMRI-derived tuning functions of direction information and whether such effects may interact with age.

2. Materials and methods

2.1. Participants

This study was part of a larger project in which the same participants performed multiple tasks, including a sequential decision making task and a virtual reality spatial memory task inside the scanner and other decision tasks outside of the scanner.

Here, we only report results from the MRI analysis of the VR task described below. Specifically, following our previous publication (Koch et al., 2020), our analyses were specific to neural representations of direction signals during the spatial memory task performed while undergoing fMRI. Other data from the same participants was not within the purview of this study and was therefore not investigated. Data of 102 participants which were recruited for two MRI sessions and randomly assigned to one of the two drug intervention groups (i.e., L-DOPA – Placebo or Placebo – L-DOPA) was available for investigating our research question. Eighty-eight of these participants (43 OA, 45 YA) successfully completed both sessions without technical errors. Four additional OA were excluded from further analyses because they did not respond in at least a third of the trials in at least one of the two sessions. Decoding analyses of the L-DOPA effects introduced additional requirements for the distribution of walking direction (see Materials and Methods) that were not met for four participants (2 OA, 2 YA). Thus, the final effective sample for these analyses also excluded these participants and comprise of a total of 37 OA (age 65–75, 6 female) and 43 YA (age 26–35, 16 female).

Note that the relatively low number of female OA reflects difficulties in recruitment after the onset of the COVID-19 pandemic.

2.2. Virtual reality task

During each session of fMRI data collection participants had to complete a similar variant of a spatial memory task that was used in previous studies (Schuck et al., 2015; Thurm et al., 2016). Analyses of the present work are mainly concerned with directional signals obtained during free navigation, and hence focus on the corresponding task phases. Specifically, to avoid effects of changed environmental cues on directional signals (e.g. Taube et al., 1990) or initial learning, we considered only data from the feedback phase for this study (see below). On average, the included data reflected a period of 17.36 min from free navigation per session.

Briefly, participants were placed in a virtual, circular arena in which they could move around freely using a custom-made MRI-compatible joystick. The arena consisted of a circular grass plane surrounded by a wall. Participants could also see distal cues (mountains, clouds) as well as a local cue (traffic cone) to aid orientation (see Fig. 1). We asked participants to remember the location of five objects within the 360° arena. First, an initial encoding phase took place in which participants could see and walk to the locations of all objects appearing one after the other. Learning of object location then continued in a feedback phase: participants were placed close to the center of the arena with a random heading direction. After the brief presentation of a grey screen and fixation cross, a picture of the first object was shown. Participants were asked to navigate as closely as possible to the location of this object and indicate their final position with a button press within a maximum of 60 s. To provide feedback, the true object location was shown to participants following their response, and they were then asked to navigate to and walk over the shown location. After the feedback, participants were shown another object and the procedure repeated without placing the player in the center of the arena until all five objects were completed. The order in which the five objects were shown was pseudo-randomized. Once all five objects were completed, participants were again placed close to the arena's center and had to navigate to all five objects in the same manner for a total of six repetitions (i.e., $5 \times 6 = 30$ feedback trials). In a final transfer phase of the task (data not analyzed in this study, see above), either the arena size or the location of the traffic cone were altered, and participants' object location memory was tested again as above. For the second session participants had to learn the location of five different objects, but the trial structure and procedures were identical otherwise. Completing one session took participants between 14 and 49 min.

2.3. Drug administration

Following a double-blind drug administration design, participants were given either a total of 225 mg of L-DOPA (Madopar, Roche, Levodopa/Benserazid, 4:1 ratio) or a placebo (P-Tabletten white 8 mm Lichtenstein, Winthrop Arzneimittel) before each MRI session in the

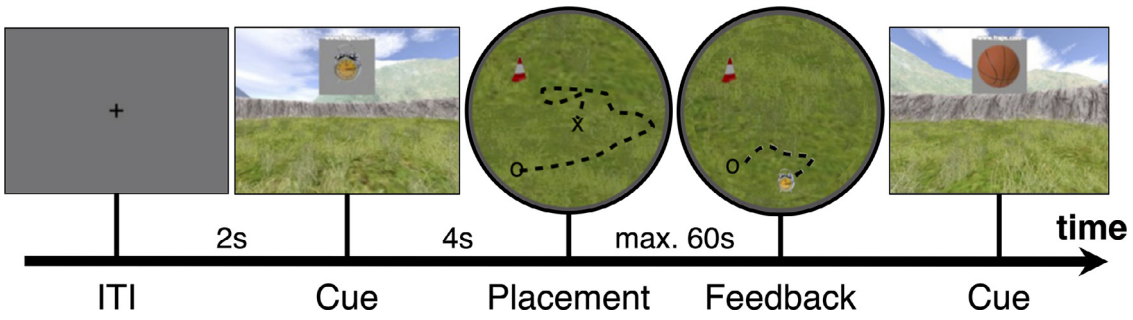

Fig. 1. Task procedure during feedback phase. Each trial started with a fixation cross on a grey background for two seconds. Afterwards a cue was presented showing the object to which participants needed to navigate (object locations were learned during encoding phase). The participant then had 60 s to navigate from their starting location (cross) to the object location according to their spatial memory. Participants indicated that they had arrived at the remembered location (circle) by pressing a response button, after which the object appeared at its true location. Participants could observe the difference between their response and the correct location and were required to navigate towards and walk over the correct location, before the cue of the next trial was presented.

form of two orally administered dosages. A first dosage (150 mg L-DOPA/Placebo) was given about 10 min before subjects entered the MRI scanner, roughly one hour before the spatial navigation task began. To assure high dopamine availability during the task, a second booster dosage (75 mg L-DOPA/Placebo) was administered roughly ten minutes before task onset (cf. Kroemer et al., 2019). Participants were pseudo-randomly assigned to one of two groups with different session order, either the group that received L-DOPA in the first session and placebo in the second session (Drug-Placebo group, 40 subjects) or the group that started with the placebo in the first session (Placebo-Drug group, 44 participants).

2.4. Image acquisition

All data was collected on a 3 Tesla Siemens Magnetom Trio (Siemens, Erlangen, Germany) MRI scanner. T1-weighted structural images were collected at the beginning of the first session using a MP-RAGE pulse sequence ($0.8 \times 0.8 \times 0.8\,mm$ voxels, TR = $2400\,ms$, TE = $2.19\,ms$, TI = $1000\,ms$, acquisition matrix = $320 \times 320 \times 240$, FOV = $272\,mm$, flip angle = 8°, bandwidth = $210\,\frac{Hz}{Px}$). At the beginning of the second session T2-weighted structural scan was collected ($0.8 \times 0.8 \times 0.8\,mm$ voxels, TR = $3200\,ms$, TE = $565\,ms$, acquisition matrix = $350 \times 350 \times 2630$, FOV = $272\,mm$, bandwidth = $744\,\frac{Hz}{Px}$).

Functional on-task data was collected using a T2*-weighted echo-planar imaging (EPI) pulse sequence ($3 \times 3 \times 2.5\,mm$ voxels, slice thickness = $2.5\,mm$, distance factor = 20%, TR = $2360\,ms$, TE = $25\,ms$, image matrix = 64×64, FOV = $192\,mm$, flip angle = 80°, 48 axial slices, GRAPPA parallel imaging, acceleration factor: 2, interleaved acquisition). The sequence lasted until the task was completed and took about 15–50 min. Additional functional scans not analyzed in this manuscript included data from the transfer phase, data from a decision making task, as well as data from a resting state scan collected at the start of each session.

Quality of all collected functional sequences was assessed using MRI quality control (MRIQC; Esteban et al., 2017). The quality measure of framewise displacement (FD, threshold 3 mm), a measure for movement during image acquisition (Power et al., 2014), was extracted and used for statistical control.

2.5. ROIs

Each ROI was created from anatomical labels obtained from Mindboggle's FreeSurfer-based segmentation of each participant's individual T1-weighted images (Klein et al., 2017). We investigated three predefined ROIs in light of previous findings indicating direction selective coding in these regions (Cacucci et al., 2004; Flossmann and Rochefort, 2021; Guitchounts et al., 2020; Koch et al., 2020; Shine et al., 2016; Taube, 2007). An early visual cortex (EVC) ROI, consisting of the bilateral cortical masks of the cuneus, lateral occipital cortex, and the pericalcarine cortex (mean number of voxels: 1480.87). A ROI of the retrosplenial cortex (RSC) constructed from the bilateral, cortical masks of the cingulate ishtmus (mean number of voxels: 198.55). A mask of the hippocampus (HC) was extracted from the respective bilateral masks of the parcellation (mean number of voxels: 323.64). In addition to these core masks, we added a ROI of the left motor cortex, constructed from the cortical mask of the left precentral gyrus, to serve as a control (mean number of voxels: 555.45). Although our resolution was suboptimal to investigate small areas, we included a mask of the entorhinal cortex (EC, mean number of voxels: 174.09) in order to explore if direction signals could be found there as well (see Inline Supplementary Table S1 for all ROI sizes).

2.6. Image preprocessing

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Results included in this manuscript come from preprocessing performed using *fMRIPrep* 20.0.6 (Esteban et al., 2018a; Esteban et al., 2018b; RRID:SCR_016216), which is based on *Nipype* 1.4.2 (Gorgolewski et al., 2011; Gorgolewski et al., 2018; RRID:SCR_002502). The boilerplate text in this section (2.6) was automatically generated by fMRIPrep with the express intention that users should copy and paste this text into their manuscripts *unchanged*. It is released under the CC0 license.

Anatomical data preprocessing

The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with `N4BiasFieldCorrection` (Tustison et al., 2010), distributed with ANTs 2.2.0 (Avants et al., 2008; RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the `antsBrainExtraction.sh` workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using `fast` (FSL 5.0.9; RRID:SCR_002823; Zhang et al., 2001). Brain surfaces were reconstructed using `recon-all` (FreeSurfer 6.0.1; RRID:SCR_001847; Dale et al., 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438; Klein et al., 2017). Volume-based spatial normalization to two standard spaces (MNI152Lin, MNI152NLin2009cAsym) was performed through nonlinear registration with `antsRegistration` (ANTs 2.2.0), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *Linear ICBM Average Brain (ICBM152) Stereotaxic Registration Model* (Mazziotta et al., 1995; TemplateFlow ID: MNI152Lin), *ICBM 152*

Nonlinear Asymmetrical template version 2009c (Fonov et al., 2009; RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym).

Functional data preprocessing

For each of the 4 BOLD runs collected per subject (two task related runs reported here and 2 resting state runs not reported here), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Susceptibility distortion correction (SDC) was omitted. The BOLD reference was then co-registered to the T1w reference using `bbregister` (FreeSurfer) which implements boundary-based registration (Greve and Fischl, 2009). Co-registration was configured with six degrees of freedom. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using `mcflirt` (FSL 5.0.9; Jenkinson et al., 2002). BOLD runs were slice-time corrected using `3dTshift` from AFNI 20160207 (Cox and Hyde, 1997; RRID:SCR_005927). The BOLD time-series were resampled onto the following surfaces (FreeSurfer reconstruction nomenclature): *fsnative, fsaverage*. The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying the transforms to correct for head-motion. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152Lin space*. The first step in this process was that a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al., 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*; Behzadi et al., 2007). Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 5% variable voxels within a mask covering the subcortical regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions. For aCompCor, components are calculated within the intersection of the aforementioned mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run (using the inverse BOLD-to-T1w transformation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al., 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using `antsApplyTransforms` (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels Lanczos (1964). Non-gridded (surface) resamplings were performed using `mri_vol2surf` (FreeSurfer).

Many internal operations of *fMRIPrep* use *Nilearn* 0.6.2 (RRID:SCR_001362; Abraham et al., 2014), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in fMRIPrep's documentation.

2.7. fMRI analyses

Classification of walking direction

All classification of walking direction was performed in Python (Python Software Foundation; Python Language Reference, version 3.7.8; available at http://www.python.org) and relied on `scikit-learn` (Pedregosa et al., 2011) and `nilearn` (Abraham et al., 2014). Statistical analyses and plotting was performed in R (version 4.0.3, R Core Team, 2021), using the packages `lme4` (Bates et al., 2015), `emmeans` (Lenth, 2021) and `ggplot2` (Wickham, 2016). All conducted post-hoc tests, if not specified otherwise, were corrected for multiple comparisons using Tukey correction.

Functional data was prepared for classification by smoothing images with a 3 mm FWHM kernel. Next, `nilearn`'s `signal.clean` function was used to detrend, high-pass filter ($\frac{1}{128}$Hz), de-noise (using 10 components of aCompCor) and z-standardize the time courses.

Participants' walking direction was extracted from navigated paths within the virtual environment. The complete 360°-space of direction was binned into six equally spaced bins of 60°. Classifier training examples were then constructed by taking fMRI multi-voxel patterns in response to consistent walking within one binned direction for at least one second. Hence the number of classifier examples for each participant and direction were dependent on the travelled paths and the number of direction changes (for more detail on the number of classifier examples, see SI Section 3). If the same example spanned multiple TRs (i.e., was longer than 2.36s) all TRs spanned were averaged to assure a single voxel-pattern per example. Voxel responses were taken two TRs (4.72s) after the event to adjust for hemodynamic lag. A multinomial logistic regression classifier (L2 regularization, C = 1, tolerance = 10^{-4}, 1000 maximum iterations; as implemented in `scikit-learn`) was applied to the resulting activation patterns in order to test whether walking direction could be classified. Cross-validation was done separately for L-DOPA and placebo sessions.

Each session was split into into three folds, and cross-validated decoding was performed across these folds from the same session. We ensured a balanced number of training examples for each class by upsampling underrepresented classes if necessary. A balanced accuracy score was calculated for each test set and results were pooled across all cross-validation runs. To asses above-chance classification accuracy the resulting scores were tested to exceed a chance baseline (16.66%) using one-sided, one-sample t-tests and one-sided comparisons to permutation distributions. Said distributions resulted from repeating individual classification procedures 1000 times with randomly permuted class labels in the training set. A permutation distribution of sample means was obtained by following the same averaging procedure as for the true values, just for each iteration of the permutation. To test whether classification accuracy was influenced by the various design factors (most notably, L-DOPA and age), linear mixed models (LMM) were used to asses possible main effects and their interactions. Specifically, the model included fixed main effects of intervention (L-DOPA vs. Placebo), age group (OA vs. YA), ROI (EVC, RSC, HC), and session order (L-DOPA – Placebo vs. Placebo – L-DOPA), as well as their interaction. The random effects included a participant wise intercept and random slope of intervention. For models including data only from one ROI, the random slope of intervention had to be dropped to avoid singularity (same number of random effects as there are data points).

Additionally, we included several control factors in our models: A drug dosage relative to body weight and dosage/kg × intervention interaction tested for potential effects of body weight; and an effect of framewise displacement (FD) and an FD × intervention interaction were included in the model as a nuisance variable to capture possible effects of drug-related head motion.

Influence of spatial angular difference on fMRI pattern similarity

To test if neural representations of walking direction show the same circular similarity structure as directions in geometrical space, we analysed the structure of classifiers predictions as in Koch et al. (2020). If the similarity of two fMRI patterns of two different directions is associated with their angular distance in space, this should be reflected in the probability distributions over all possible directions. Specifically, we extracted the probability estimates of each of the six classes for each example of the testing set as calculated by the logistic regression classifier. These estimates were aligned with regard to relative angular difference from the target class (−120°, −60°, 0°, 60°, 120°, 180°) and then averaged over all examples, resulting in a single curve for each participant which we refer to as the *confusion function*. A simple Gaussian curve in the form of

$$g(x) = \frac{1}{Z} e^{-\frac{1}{2}\tau x^2}, \quad (1)$$

was used to determine tuning specificity, where x denotes the angular difference and τ the precision (the inverse of the variance, $\frac{1}{\sigma^2}$). Furthermore, Z normalizes the curve. This model captures an inverse relationship between the angular difference of two walking directions and the confusability of their associated neural patterns. Models were fitted separately within each participant and ROI.

The Gaussian model allowed us to assess age-differences in directional tuning specificity, which were captured by the precision parameter τ. A LMM identical to the one modelling classification accuracy described in the previous section was used to analyze differences in precision.

2.8. Behavioral analysis

Task performance during the feedback phase was measured by the distance error: the Euclidean distance between the true location of an object and the location the participant placed the respective object (measured in virtual meters; vm; 1vm = 62.5 Unreal units). Performance for each trial was given by the average distance error across all five presented objects within a trial (missing responses due to exceeding the time limit were excluded). Kolmogorov–Smirnov tests indicated that performance scores of YA were not normally distributed ($D = 0.169$, $p = 0.010$, $D = 0.064$, $p = 0.881$, for YA and OA, respectively; tested for performance on the last trial). To assure normality, the average distance errors in each trial were log-transformed ($D = 0.054$, $p = 0.941$, $D = 0.106$, $p = 0.323$ after transform for YA and OA, respectively). To assess the process of learning during the feedback phase of the task, we compared the difference between the first and last trial. Note that in light of non-linear learning curves we did not use a linear model across all trials on purpose. The difference between the two log-transformed measures was modeled using an LMM including the fixed effects of intervention (L-DOPA vs. Placebo), age group, and session order (L-DOPA – Placebo vs. Placebo – L-DOPA) as well as a random intercept of participant. Additionally, we compared performance after learning (last trial) with an identical LMM. Furthermore, group-level performance was compared to chance given by the average distance error assuming random responses for every object. To this end, we uniformly sampled 10^5 possible locations within the circular arena. The task was then simulated 1000 times while each response of each participant was randomly drawn from the pool of possible locations. This yielded a distribution of 1000 group-means assuming random performance over a given trial and allowed a comparison of trial-specific group-means

Finally, we aimed to quantify the relationship between the specificity of direction signals and task performance to see if more specific direction signals allow better performance on the given task. To this end, we used previous LMMs of classification accuracy but added the regressor of performance in the last trial of the experiment. To assure normally distributed values the log-transformed performance variable was used. Furthermore, performance values were demeaned to eliminate a possible confound between age group and task performance. The FD-related nuisance regressors as well as the interaction between dosage per body weight and intervention were dropped from the model. To see if L-DOPA enhanced signal specificity in proportion to its enhancement of task performance the above model was adapted to predict the difference between sessions in classification accuracy (L-DOPA – Placebo). The increase in task performance was given by the session difference (L-DOPA – Placebo) of the log-transformed performance in the last trial of the task.

3. Results

3.1. Behavioral results

We first asked whether age group and intervention (L-DOPA vs. Placebo) affected participants' object location memory, as expressed in distance errors on the last trial after learning. This this end, we ran a linear mixed model with fixed effects of interest for intervention and age group and a random effect of participant. This analysis showed a significant main effect of age group ($\chi^2(1) = 167.010$, $p > 0.001$; χ^2 values reflect likelihood ratio tests, see Methods). Post-hoc tests showed that OA had higher distance errors compared to YA at the end of learning ($t(80) = 12.811$, $p < 0.001$). The model did not display any significant main effect of L-DOPA intervention ($\chi^2(1) = 1.479$, $p = 0.224$) or L-DOPA × age interaction. Results are displayed in Fig. 2.

We next investigated performance increases, i.e. log distance errors on the first minus the last trial, and again found only a main effect of age group ($\chi^2(1) = 61.054$, $p > 0.001$), but no main effect of L-DOPA or L-DOPA × age interaction. A control analysis showed that the nuisance variable session order had no main effect in either end-of-learning performance ($\chi^2(1) = 0.1784$, $p = 0.673$) or in performance changes ($\chi^2(1) = 0.948$, $p = 0.330$), and also revealed no session order × intervention effect in performance changes. Unexpectedly, we found a significant interaction of intervention × session order in end-of-learning performance ($\chi^2(1) = 13.744$, $p < 0.001$), reflecting a negative effect of L-DOPA if given in the first session ($t(80) = 3.368$, $p = 0.002$) while no effect was found if L-DOPA was given in the second session ($t(80) = -1.693$, $p = 0.180$, Ŝidák corrected).

3.2. Influence of L-DOPA intervention on direction decodability

We used within-session cross-validation to investigate the decodability of walking direction (see Methods). A first analysis revealed that, averaged across sessions, decoding in our main areas of interest EVC (23.6%), RSC (18.4%) and HC (17.3%) was above chance baseline (16.6%, one-sided t-tests against chance, $t(79) = 11.783$, $p < 0.001$, $t(79) = 4.627$, $p < 0.001$, $t(79) = 2.011$, $p = 0.047$, respectively), while it was at chance in the entorhinal cortex (16.9%, $p = 0.257$, all *ps* Bonferroni-Holm corrected for 4 ROIs). These results were largely confirmed by a permutation test, although the HC effect was borderline after correction (EVC: $p < 0.001$, RSC: $p < 0.001$, HC: $p = 0.058$, Entorhinal Cortex: $p = 0.236$, Bonferroni-Holm corrected).

Surprisingly, decoding in the left motor cortex was also above chance baseline, and significantly higher than in the HC ($t(608) = -3.672$, $p = 0.002$) and entorhinal cortex ($t(608) = -4.504$, $p < 0.001$). The high decoding score in the motor cortex was unexpected because participants used the same forward movement on the joystick to walk forward, regardless of the direction they traveled in. While we did not anticipate this effect, it indicates that this brain area cannot serve as a useful control ROI. The results of the motor cortex are depicted in greater detail in Inline Supplementary Figure S1, and will not be detailed further here. Note that correction for five instead of four ROIs does not qualitatively affect the results reported above.

Importantly, we next investigated whether classification accuracy was affected by dopamine, and indeed found a significant main effect of L-DOPA in a corresponding LMM ($\chi^2(1) = 6.796$, $p = 0.009$). This effect reflected that direction signals were generally stronger under L-DOPA than placebo (post hoc test: 19.5% vs. 18.6%, $t(74) = 2.556$, $p = 0.013$), in

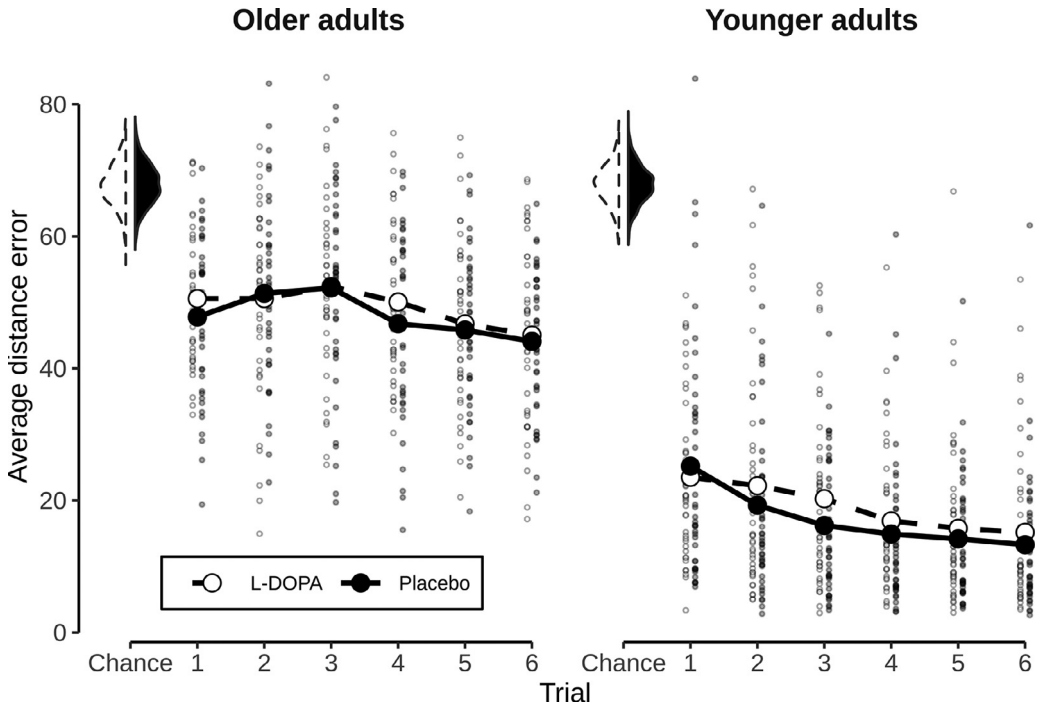

Fig. 2. Behavioral results. Average error in object placement for all six trials for OA and YA. Error was measured as the Euclidean distance in vm between the true location of an object and the participants' placement. Reduction in error shows better task performance. All values of the placebo session depicted in black, all values of the L-DOPA session depicted in white. Small dots indicate individual values of participants. Average over participants in each trial shown by the large dots. Shown on the upper left are session-specific distributions of 10^3 average performance values in a trial assuming random placement of objects. Note that, in turn, only the trial averages (large dots) can be compared to this chance-distribution.

line with our main hypothesis (see Fig. 3A). Figure 3B shows permutation tests against chance baseline within the L-DOPA and placebo conditions. These permutation tests showed that decoding was above chance in both conditions in the EVC and RSC (EVC: $p < 0.001$ & $p < 0.001$, RSC: $p < 0.001$ & $p = 0.036$ for L-DOPA and placebo, respectively) while in the HC decoding was above chance only under L-DOPA ($p = 0.010$), but not under placebo ($p = 0.884$, all ps Bonferroni-Holm corrected). Control analyses testing the influence of nuisance regressors (FD, session order, dosage) in the LMM showed no main effects or interactions with the L-DOPA intervention (all ps > 0.08). The LMM also indicated a number of other effects, in particular of age group ($\chi^2(1) = 6.273$, $p = 0.012$), ROI ($\chi^2(4) = 271.674$, $p < 0.001$), as well as an age group × ROI interaction ($\chi^2(4) = 60.970$, $p < 0.001$). But no L-DOPA × ROI or L-DOPA × age interactions were found ($p = 0.427$ and $p = 0.506$).

The main effect of ROI reflected that the classification achieved in EVC was significantly higher than decoding in the RSC ($t(608) = 10.837$, $p < 0.001$), HC ($t(608) = 13.108$, $p < 0.001$), left motor cortex (19.1%, $t(608) = 9.436$, $p < 0.001$), and entorhinal cortex (16.9%, $t(608) = -13.940$, $p < 0.001$). In addition, decoding in the RSC significantly outperformed that in the entorhinal cortex ($t(608) = -3.104$, $p = 0.017$).

Post-hoc comparisons of the age group main effect and the age group × ROI interaction showed that decoding was overall better in YA compared to OA, but this age difference was only significant in the EVC ($t(359) = -7.424$, $p < 0.001$) but not in any other ROI (ps ≥ 0.833, Ŝidák corrected) as displayed in Fig. 3C. Note that the EVC also showed age differences in the size of the ROI, as reflected in significantly lower voxel numbers in OA compared to YA ($p < 0.001$, 1583 voxels vs. 1361 voxels on average, respectively, $p < 0.001$). However, repeating the decoding analysis in a subsample of participants matched for ROI size showed equally strong age differences in decoding, indicating that age differences in decoding found in the EVC are not explained by the larger EVC ROIs in YA (see Supplementary Materials Section 1 for details).

As noted above, no L-DOPA × ROI interaction was found. Our results therefore indicate that L-DOPA impacts the neural encoding of direction signals across a variety of brain regions. The following analyses therefore need to be seen as strictly exploratory. These exploratory follow-up analyses showed that the L-DOPA effect was strongest in the HC ($t(603) = 2.153$, $p = 0.032$), while post-hoc test in RSC and EVC revealed only marginal ($t(603) = 1.916$, $p = 0.055$), or non-significant effects ($t(603) = 1.447$, $p = 0.148$), respectively (all ps uncorrected). Neither the left motor cortex nor the entorhinal cortex did show any effects of L-DOPA ($t(603) = -.211$, $p = 0.833$, $t(603) = 0.710$, $p = 0.478$, both uncorrected). To further explore trends in region-specific effects of L-DOPA, and interaction with age group therein, analyses were run separately for each ROI. These ROI-specific models reproduced the main effects of intervention within the HC ($\chi^2(1) = 5.263$, $p = 0.022$) and the RSC ($\chi^2(1) = 4.868$, $p = 0.027$). In addition, we found an intervention × age group interaction within the RSC ($\chi^2(1) = 3.877$, $p = 0.049$), but no such interaction in HC ($\chi^2(1) = 1.518$, $p = 0.218$, see Fig. 3D). Post-hoc comparisons showed that the effect in RSC was driven by higher decodability of walking direction in the L-DOPA compared to placebo session in young adults ($t(75.6) = 2.879$, $p = 0.010$), but not in OA ($t(75.4) = -.161$, $p = 0.984$, Ŝidák corrected). Within the EVC, only a main effect of age group ($\chi^2(1) = 16.350$, $p < 0.001$), but no effect of L-DOPA intervention ($\chi^2(1) = 2.038$, $p = 0.153$) was found.

Control analyses found no impact of dosage per body weight on the intervention effect in any ROI ($\chi^2(2) < 3.578$, $p \geq 0.167$, for the interaction). Investigating the movement related variable FD, we found no significant main effects of FD ($\chi^2(1) \leq 1.448$, $p \geq 0.229$) or an interaction between FD and intervention ($\chi^2(1) \leq 0.644$, $p \geq 0.422$) in HC or RSC. A significant main effect of FD was found in the EVC, however ($\chi^2(1) = 4.935$, $p = 0.026$). This reflected worse classification accuracy with higher movement during image acquisition (linear regression relating classification accuracy to FD: $b = -.118$, $t(158) = -6.302$, $p < 0.001$). A final control analysis within the left motor cortex did neither identify a

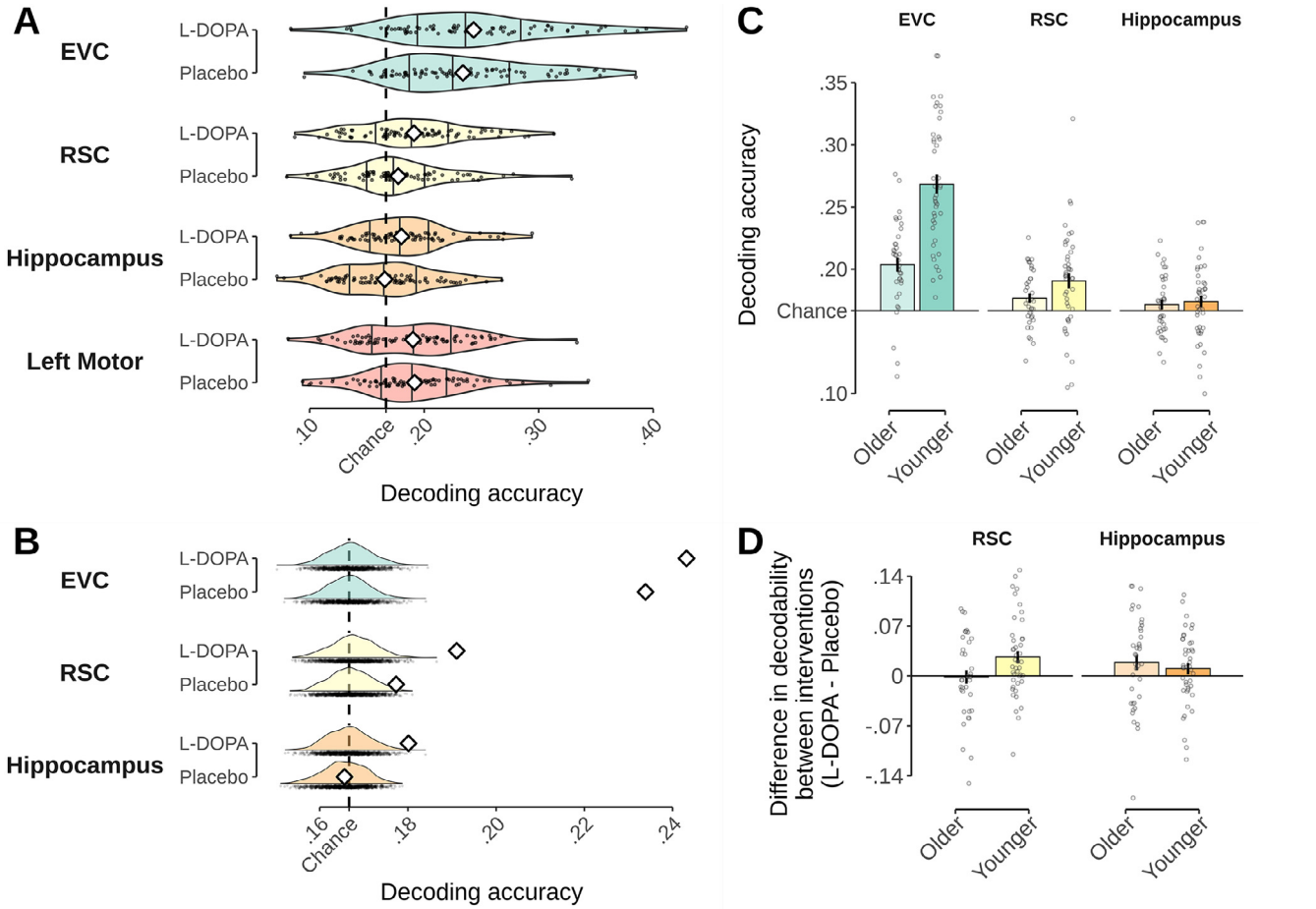

Fig. 3. Effect of L-DOPA on decoding of neural walking direction signals. **A**: Intervention-specific decodability of walking direction within each ROI. Black dots show values of participants and violin plots depict intervention-specific distribution. Means are represented by white diamonds. Chance-level is shown by dashed line and based on the total number of classes (6 classes, 16.6% chance). **B**: Intervention-specific decodability of walking direction compared to chance baseline. Mean decodability in the sample shown as white diamonds. Distributions of 1000 sample means given shuffled labels during classifier training serve as chance baseline. Chance-level is shown by dashed line. **C**: Age group-specific decodability of walking direction. Dots show individual values of participants and bars show group averages. Error bars depict standard error of the mean. **D**: Influence of drug intervention on decodability (L-DOPA – Placebo) shown for the RSC and hippocampus and split by age groups. Values higher than zero indicate higher decoding accuracy in the L-DOPA condition. Bars reflect group means and error bars reflect SEM. Black dots show individual values of each participant.

main effect of intervention ($\chi^2(1) = 0.027$, $p = 0.869$) nor any other main effects. Post-hoc tests confirmed that direction decodability in motor cortex under L-DOPA was not significantly different from decodability under placebo, regardless of session order ($t(74.9) = -1.519$, $p = 0.133$, and $t(74.1) = 1.202$, $p = 0.233$, L-DOPA – Placebo and Placebo – L-DOPA, respectively).

3.3. Relations between task performance, L-DOPA and direction decoding

Following up on the above results, we asked whether neural direction encoding was related to task performance, and whether this relation was affected by L-DOPA. We therefore investigated the link between session-specific decoding accuracy and task performance (spatial distance error) on the last trial, in addition to age group and intervention. Because performance on the last trial was highly confounded with age group (see Fig. 2) performance values were demeaned within each age group to investigate effects unrelated to age-specific performance differences.

A model within the EVC revealed a significant main effect of distance error on the last trial on direction decoding ($\chi^2(1) = 7.594$, $p = 0.006$, $b = 0.040$; see Fig. 4A), pointing towards better decoding accuracy with better task performance. The relation between task performance and EVC decoding also interacted with age group ($\chi^2(1) = 3.921$, $p = 0.048$), reflecting that the above mentioned relationship was present in YA ($F(1, 111.03) = 11.912$, $p < 0.001$, $b = 0.033$) and absent in OA ($F(1, 121.83) = 0.066$, $p = 0.798$, $b = 0.006$, both uncorrected). As expected the model of EVC decoding accuracy also displayed a main effect of age group ($\chi^2(1) = 40.244$, $p < 0.001$; see results for influence of L-DOPA on decoding accuracy). No effects related to task performance were found in the RSC or the HC ($ps \geq 0.053$).

We next investigated change-change relations, asking whether L-DOPA-related changes in decoding were related to L-DOPA-related changes in task performance (see Fig. 4B). Linear regressions revealed that in YA L-DOPA-related changes in direction decoding in EVC were indeed positively related to changes in task performance ($F(1, 72) = 6.730$, $p = 0.011$, $b = -.053$, uncorrected, negative slopes since performance increase means less errors). In OA, this was not the case ($F(1, 72) = 0.049$, $p = 826$, $b = 0.006$, uncorrected). Linear models within the RSC and HC did not show any significant effects in change-change relations. Hence, our results reveal that in EVC better direction decoding was related to better task performance. Moreover, the more L-DOPA improved direction decoding in EVC, the more participants improved on the task from the place to the L-DOPA session, in particular among younger adults.

A analysis of nuisance variables in EVC showed that there was no main effect of session order ($\chi^2(1) = 0.009$, $p = 0.922$), although

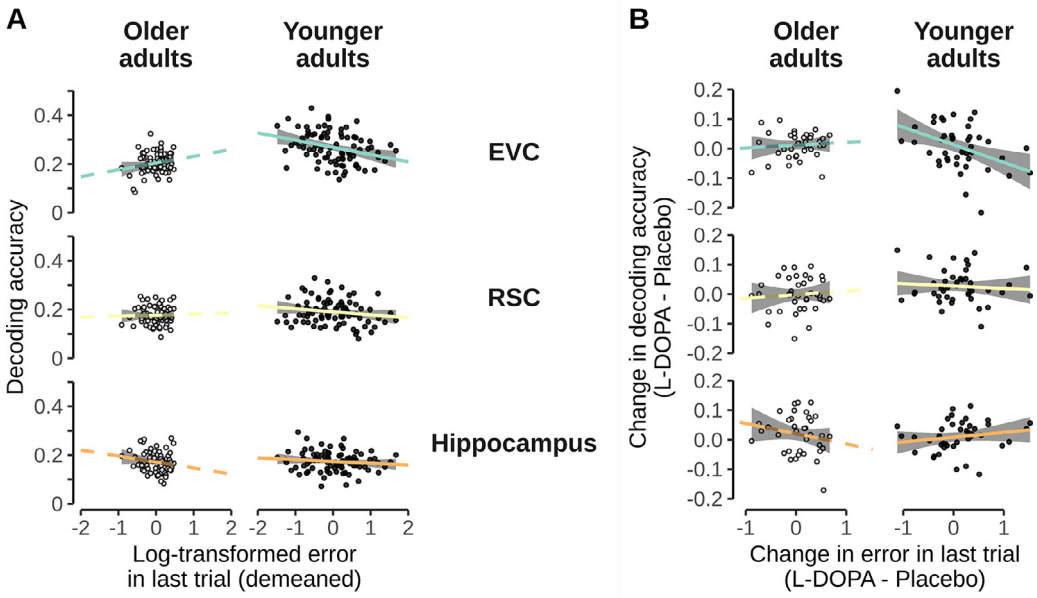

Fig. 4. Relationship between decoding accuracy and behavioral performance. **A**: Relationship between decoding accuracy and log-transformed and demeaned distance errors. Shown for the EVC, RSC, and hippocampus separately for both age groups. Dots represent individual participants where OA are shown in white. Lines represent linear models of represented subset and are colored according to the ROI and shown in dashed for OA. **B**: Drug-related change-change relationship between decoding accuracy and behavioral performance. Axes show influence of L-DOPA administration by showing the difference in values between the L-DOPA session and placebo session. Depiction accordingly to A. Please note that in both, A and B, the slope lines were extended beyond the data points purely to aid visibility.

a interaction between task performance and session order emerged ($\chi^2(1) = 4.332$, $p = 0.037$). A post-hoc test revealed a trend towards differing slopes depending if L-DOPA was given in the first or second session ($t(132) = 1.904$, $p = 0.059$) but separate tests within each session order did not display any significant relationships between performance and classification accuracy ($F(1, 143.83) = 0.607$, $p = 0.437$, $F(1, 118.80) = 3.164$, $p = 0.078$, for L-DOPA – Placebo and Placebo – L-DOPA, respectively).

3.4. Influence of L-DOPA intervention on tuning specificity

Finally, we investigated whether L-DOPA also affected tuning width, i.e. the how often neural signals encoding nearby directions where confused with each other.

Omnibus analyses across the main ROIs revealed no L-DOPA effect, a main effect of ROI ($\chi^2(2) = 281.509$, $p < 0.001$), and results otherwise consistent with those reported below. We therefore immediately report results of ROI-specific LMMs. A model of EVC tuning width found no main effect of intervention or intervention × age effect. We did find a significant main effect of age group ($\chi^2(1) = 20.631$, $p < 0.001$), reflecting lower precision of the fitted Gaussian curves in OA compared to YA ($t(79.7) = -4.533$, $p < 0.001$). The same analyses in RSC and HC showed no significant main effects of intervention, age, or intervention × age interactions. The means of the fitted Gaussian curves in the L-DOPA condition are shown in Fig. 5B. Hence, L-DOPA did not have any effects on tuning functions in any of the investigated ROIs.

No nuisance effect of FD, session order, or FD × intervention interaction were found in any ROI-specific model ($\chi^2(1) \leq 0.857$, $p \geq 0.355$; $\chi^2(1) \leq 0.257$, $p \geq 0.612$, and $\chi^2(1) \leq 0.578$, $p \geq 0.447$, respectively). Additionally, intervention was not involved in any interaction with dosage per body weight ($\chi^2(2) \leq 4.412$, $p \geq 0.110$). Unexpectedly, however, we found a significant intervention × session order interaction in the EVC ($\chi^2(1) = 10.713$, $p < 0.001$; see Fig. 5A), suggesting that tuning precision was higher when L-DOPA was administered in the second session ($t(74.0) = 2.911$, $p < 0.009$) compared to when it was administered in the first session ($t(75.2) = -1.607$, $p = 0.212$). No intervention × session order interaction was found in any other ROI.

4. Discussion

In this work we tested the impact of L-DOPA on neural representations of walking direction in younger and older adults, using a double-blind, cross-over intervention design. In addition to a classic decoding approach, we assessed direction specificity of neural signals, a proxy for tuning functions, using the relative structure of classifier probability estimates. Our results revealed that decodability of walking direction signals across all ROIs was enhanced following the administration of L-DOPA. Although no interaction between ROI and L-DOPA was found, post-hoc analyses hinted numerically at stronger effects in HC and RSC. Interestingly, however, task performance (spatial distance error) was related to EVC direction decoding in younger adults, and L-DOPA related changes in EVC decoding were related to changes in the same spatial memory measure. Moreover, these results showed that L-DOPA had comparable effects on HC walking direction signals in both age groups, but in the RSC these DA effects were present only in YA. An investigation of tuning specificity revealed no main effects of L-DOPA or L-DOPA × age group interactions.

Investigating age group differences, we found higher classification accuracy and precision of tuning functions in the EVC of YA compared to OA, a sign of neural dedifferentiation. No age effects on decoding in the HPC or RSC were found. These results confirm our previous finding that neural representations of walking direction can be found in EVC and RSC, and that strong age-related differentiation is present particularly in EVC Koch et al. (2020). We also showed that better EVC classification accuracy was related to better performance on task, suggesting an important functional role of this area in our task.

Importantly, our results also offer a number of novel insights. First, we show a causal influence of L-DOPA on how walking directions are encoded in the brain. No statistical evidence for ROI difference were found, but the pattern of results suggests that this effect was mainly driven by effects in the HC and the RSC. Hence, further investigations are needed in this regard. Both areas have been linked to directional and other spatial information (Burles et al., 2017; Shine et al., 2016; Spiers and Barry, 2015), and have even been shown to be part of the same dorsal pathway involved in visuospatial processing (Kravitz et al., 2011). Addition-

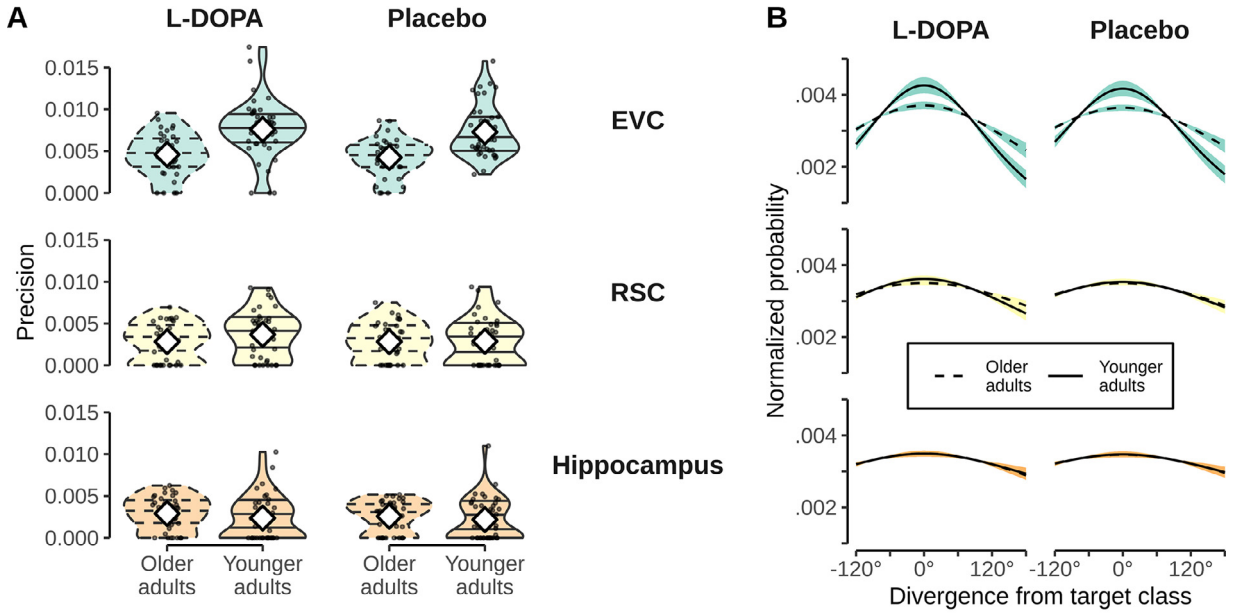

Fig. 5. Effect of L-DOPA on tuning specificity. **A**: Precision of Gaussian curves fitted to individual confusion functions in both age groups. Shown separately for the L-DOPA and placebo intervention in the EVC, RSC, and Hippocampus. Black dots show values of individual participants. Intervention-specific distributions are shown by violin plots. White diamonds depict means. Plots of OA shown in dashed lines for easier distinction. **B**: Mean Gaussian tuning curves shown separately for age groups and intervention (L-DOPA vs. Placebo). ROI separation identical to that of panel A. OA are depicted with dashed lines. Shaded area represents SEM and is colored according to ROI. For each participant a Gaussian curve was fitted to the individual confusion function (given by the classifier). The shown mean Gaussian curves were obtained by averaging participants' individual Gaussian curves.

ally, both areas display dopaminergic innervation (Berger et al., 1985; McNamara and Dupret, 2017), and previous reports have linked DA and spatial cognition more generally (El-Ghundi et al., 1999; Granado et al., 2008; Thurm et al., 2016). Notably, hippocampal decoding in the placebo session was at chance in both age groups, and only significant during the L-DOPA intervention. While the lack of decoding effects under placebo observed here might suggest that the human hippocampus under normal circumstances does not bear any information about traveling direction, this interpretation seems unlikely in light of the large literature suggesting otherwise (see Spiers and Barry, 2015, for a review). We therefore believe that the lack of effect may be due to issues of statistical power and noise in the data. In contrast to the placebo condition, the significant decoding results in the L-DOPA condition suggests that L-DOPA may have amplified existing directional signals in the hippocampus, rather than causing previously non-existent signals to appear de novo.

Second, the positive effects of DA on decoding are in line with computational models and empirical findings which suggest that DA affects neuronal gain (Cohen and Servan-Schreiber, 1992; Li and Rieckmann, 2014; Thurley et al., 2008). Accordingly, DA's influence on neural gain could lead to a stronger separation between signal and noise, which made different stimuli more specific and easier to distinguish for the classifier. It should be noted, however, that we did not find any direct effects of L-DOPA on neural direction tuning specificity, which measures how similar neural patterns are to similar directions. Given the effects of DA on neural gain, we had hypothesized that this measure could be more sensitive to the effects of our intervention, but this was not the case. One possible explanation is that our design lacked the power to fully capture the neural tuning functions within just one session. Tentative analyses of EVC and RSC tuning specificity did show DA-related enhancement only in participants who received L-DOPA in the second session. We will discuss these session-specific effects further below. Third, our study was set up to ask whether the L-DOPA intervention might reduce age-related neural dedifferentiation. Virtual walking direction offered a promising window to answer these questions since it has previously been shown to be subject to age-related neural dedifferentiation (Koch et al., 2020) and the broader domain of spatial cognition has been shown to be highly age-sensitive (Lester et al., 2017; Wolbers et al., 2014). Age is also known to cause substantial loss of DA functioning (e.g. Bäckman et al., 2006), and we speculated that a lower baseline DA availability might magnify the effects of L-DOPA. Surprisingly, we did not find that the effects of L-DOPA were particularly pronounced in OA. Rather, the HC showed age-equivalent effects, and decoding in RSC was in fact enhanced only in YA.

Other than individual differences in baseline DA level, task demand may also affect the inverted-U function of DA modulation (Cools and D'Esposito, 2011). The spatial navigation task used in our study is quite demanding, such that YA though have higher baseline DA level could still benefit from the L-DOPA intervention, whereas in OA the task demand may still outweigh the benefit of L-DOPA intervention. While unexpected, these results could offer interesting insights into the complexity of how external DA medication might interact with neural differentiation and compensatory plasticity mechanisms that counteract age-related losses. One notable aspect in this regard is that we found no evidence of age-related dedifferentiation in HC or RSC, which speculatively could be a sign of compensatory mechanisms. It seems possible that DA interventions might only recover neural specificity in brain areas that are affected by age-related dedifferentiation. Contrary to this idea, we found no age-related L-DOPA effects in visual cortex, where dedifferentiation was observed – but this might be due to the relatively low D2 receptor density in this area (Lidow et al., 1989). Another possibility is that we did not observe age-specific effects of L-DOPA on neural direction encoding in RSC and HC for the same reasons we did not find age-related dedifferentiation in these regions. According to this idea, compensatory factors that have mitigated dedifferentiation also affected the effectiveness of external dopamine administration, for instance because of changed connectivity. Both ideas remain speculative and further studies are needed to fully understand how the effects of L-DOPA interventions on neural direction encoding interact with age and dedifferentiation.

Beyond these main implications, a number of interesting observation arose that warrant further investigation. Although we did not find any main effects of session order, we found some indications that session order could influence the effect of L-DOPA on neural signals that underlie spatial navigation. Age-differences in learning were stronger when L-DOPA was administered in the second compared to the first session. In addition, we found tuning specificity in EVC and RSC to be enhanced by L-DOPA only in participants who received the drug in the second session. Stronger effects when DA is administered in a second session have previously been reported in the context of spatial navigation (Thurm et al., 2016). The reason why session order effects could exist in this context are numerous. Garrett et al. (2015), for instance, highlight two possible explanations in the context of DA effects on neural signal variability. One is that previous training may increase the amount of baseline DA-release, based on findings in rodents (Owesson-White et al., 2008). A DA intervention could therefore lead to differing DA-availability depending on whether the participants had already been trained with the same or a similar task. A second possible explanation raised by Garrett et al. (2015) is that the environment is either learned in a state of higher or normal DA-availability. The state of the second sessions will consequently always be mismatched to the first session, leading to effects of drug administration given the respective session. Related to the first idea, we speculate that in our case general learning about the environment in a first placebo session could have established beneficial baseline for the effects of L-DOPA in the second session. Unfortunately, the present design is unfit to address such explanations and further evidence is warranted.

One open question is why the effect of L-DOPA on decoding in HC and RSC was not reflected in task performance, where no L-DOPA effect was found. In addition to generally small effects on neural representations, another explanation might be that task performance did not only depend on direction signals, but also relies on distance estimation and using distal and local cues, processes which themselves are affected by age (Schuck et al., 2015). The task might therefore have been too complex to provide a suitable behavioral measure. Interestingly, however, we did find some relationships between behavior and the specificity of directional information in visual cortex, indicating that neural markers might have different relations to performance in our task. This is shown by some of our results that also offer insights about age-related changes in the context of spatial navigation more generally. The results in the EVC showed that OA exhibit lower precision of directional tuning functions. This is a replication of findings reported in an earlier study using a similar analysis approach (Koch et al., 2020). During natural navigation and the perception of direction vision plays a major role as it allows stable directional signals (Goodridge, 1998) and corrects and prevents the accumulation of errors during path integration (Jeffery, 2007). A less precise visual signal in OA could therefore influence spatial signals downstream and contribute towards the pronounced difficulties OA have in spatial tasks. Interestingly, we also found a relationship between EVC direction decoding in YA and performance on task, suggesting better spatial memory performance if walking direction could be decoded with higher accuracy. While this concurs with previous reports of a link between (non-spatial) memory and signal specificity (Koen et al., 2019; Sommer et al., 2019; St-Laurent et al., 2014), previous studies have mostly reported such links in older adults. Future work is required to further understand how age-related loss in specificity of visual signals might be involved in spatial cognition. That said, a simple propagation of less specific visual signals to the retrosplenial complex network seems unlikely, since there was no evidence for age-related dedifferentiation in the RSC or HC.

We would also like to point out a set of limitations that should be considered when interpreting the results of the presented work. While our results were statistically significant, and decoding performance compared to chance was broadly in line with previous studies (e.g. Koch et al., 2020; Shine et al., 2019), the reported classification of direction signals remained numerically low in all ROIs. The substantial amount of wrong predictions of the classifiers even in the intervention session could indicate that effects of L-DOPA were small. We speculate that other factors influenced the BOLD signals that are unrelated to direction, including aspects related to vasculature, context or learning sensitivity of neural signals, and mixed selectivity of neural populations. In combination with a rather small number of training examples within each intervention session, this could explain the weak classifier performance. A second limitation is that the reported results come from a largely male sample, which questions whether our results generalize to women. Given the small sample size, the presented data also does not allow to draw conclusions regarding sex differences in spatial navigation, which have been reported in some (e.g. Andersen et al., 2012; Spriggs et al., 2018; see Brake and Lacasse, 2018 for a review), but were absent in other studies (Bohbot et al., 2012; Levy et al., 2005; Rodgers et al., 2012). Another unexpected result was that we found substantial decoding performance in motor cortex. This is surprising given the fact that no one-to-one mapping between motor actions (joystick movement) and walking direction should exist (participants used the same forward movement on the joystick to walk forward, regardless of the direction they traveled in). One possible explanation is that joystick tilt was systematically related to travel direction, which would explain why this brain area carried direction information. Indeed, given that brain correlates of sensorimotor signals are often stronger and less noisy than correlates of abstracted quantities, the relative strength of decoding seems less surprising. In addition, this result may also speak to the fact that spatial navigation is supported by a wide network of brain areas, and hence a true control area might be less readily available. Of note, this decoding does also not seem to reflect an inflated chance baseline, since other areas showed no or significantly lower decoding, and no effect of L-DOPA in motor cortex was found (see SI Section 2). Future work is required to address these limitations and to in turn build a more concise framework in which our findings can be embedded.

In summary, we provide first causal insights into the role of dopamine in the encoding of spatial direction signals in the human brain. In addition, as suggested by exploratory data analysis, this enhancing effect of dopamine on the specificity of neural signals involved in navigation might mainly be present in the hippocampus and in the retrosplenial cortex, albeit there exclusively in younger adults. In combination with the replication of our own previous results (Koch et al., 2020), these findings offer insights into the neural processes underlying spatial navigation in the human brain, and how they are affected by age more generally.

Data and Code availability

All code of the involved analyses will be published and made openly available at https://github.com/koch-means-cook/damson.

The data supporting the findings of this study will be shared in preprocessed or aggregated form that ensures full anonymity of subjects, in line with funding and ethical regulations. Given the drug intervention and double blind nature of this work, the precise constraints on data sharing are currently evaluated.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at 10.1016/j.neuroimage.2022.119670

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Supplementary Information

for

L-DOPA enhances neural direction signals in younger and older adults

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1 Relationship between ROI size and classification accuracy

Each ROI was created from anatomical labels obtained from Mindboggle's FreeSurfer-based segmentation of each participant's individual T1-weighted images (Klein et al., 2017). Since the segmentation was conducted on individual images, the amount of voxels included in each ROI (i.e. size) varied between participants. Average size and variation of each ROI can be found in Table S1.

Table S1: Sample-average and standard deviation of number of voxels included in each ROI.

ROI	Mean number of voxels	SD
Entorhinal Cortex	174.09	27.86
EVC	1480.87	232.09
Hippocampus	323.64	28.68
RSC	198.55	32.14
Left Motor	555.45	71.59

As a control analysis we wanted to check if the number of voxels available for each subject within each ROI influenced classification accuracy. We set up five separate linear models, one for each ROI, relating classification accuracy to the number of voxels used to train and test the classifier (both variables z-scored). Decoding was significantly related to the number of voxels in EVC ($\beta = .342$, $R^2_{adj} = .106$, $F(1, 78) = 10.37$, $p = .002$, uncorrected) but no other ROI ($ps \geq .124$, uncorrected). Specifically, the model described a positive relationship so that higher classification accuracy was accompanied by a larger EVC ROI. The relationships are shown in Fig. S1.

Since the EVC was also the only ROI in which we reported age differences in classification accuracy, we investigated if this age difference in the EVC was related to differences in ROI size. Indeed, a two-sided t-test showed that older adults had smaller EVC ROIs compared to older adults (mean number of voxels OA: 1361.324, YA: 1583.744, $t(70.432) = -4.79$, $p < .001$). To test whether these age difference could explain age differences in classification, we created a subsample of 25 older and 25 younger participants with matched numbers of voxels within the EVC ROI. Specifically, we selected the 25 older adults with the highest voxel counts and then

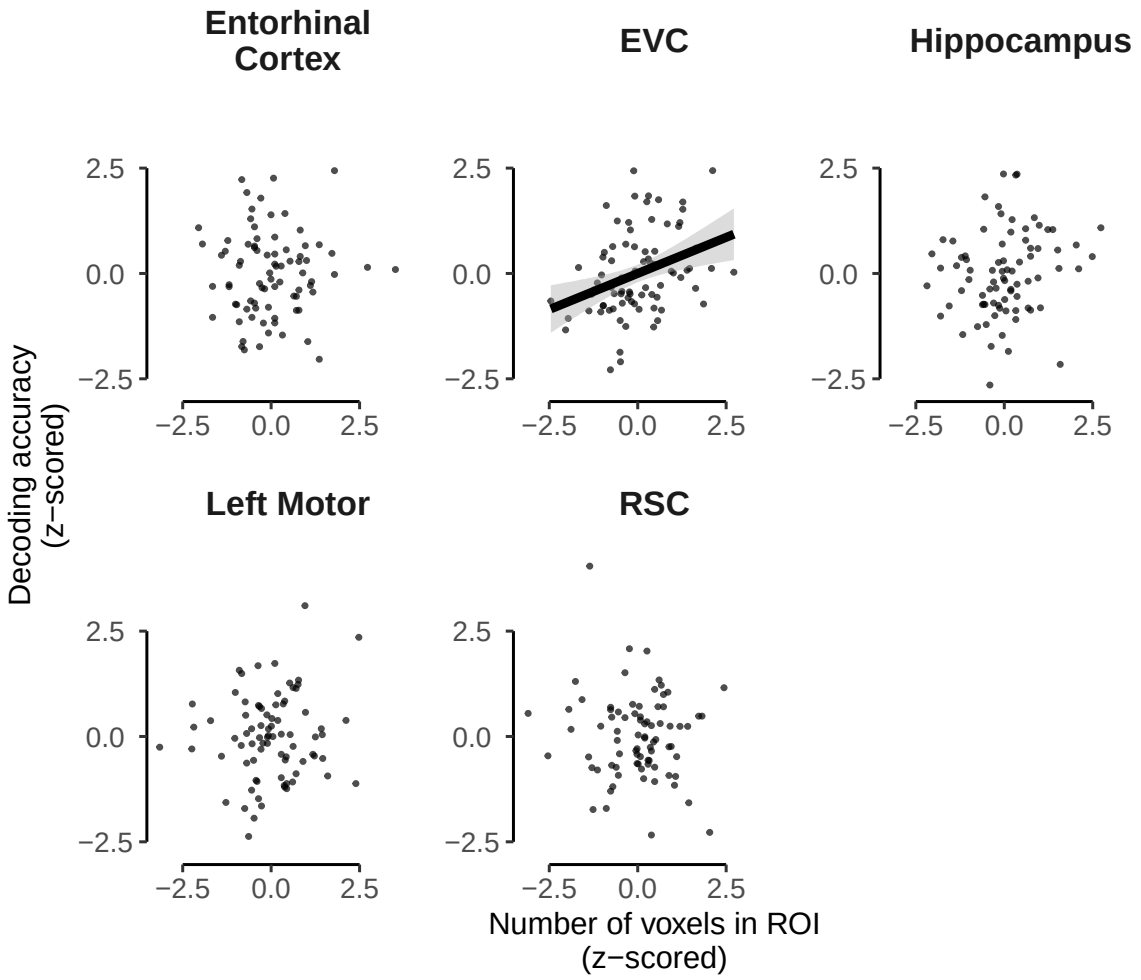

Figure S1: Linear relationship between decoding accuracy and number of voxels within each ROI (both variables z-scored within each ROI). Dots represent individual participants. Regression lines are only displayed for significant relationships.

picked 25 matched younger adults with the closest amount of voxels in the mask. This resulted in more comparable ROI sizes (older adults: 1463.56 voxels, vs. 1489.64 voxels in younger adults, $t(47.56) = -0.512$, $p = .612$). Importantly, a two-sided t-test still showed a significantly lower classification accuracy in older adults in the matched sample (diff = -.073, $t(45.25) = -5.62$, $p < .001$). We therefore conclude that the age differences in decoding found in the EVC are unlikely to be an artifact of larger EVC ROIs in younger adults.

2 Classification accuracy in left motor cortex

Permutation tests showed that average classification accuracy of direction across both sessions was significantly above chance in both age groups (OA: 18.5%, $p < .001$, YA: 19.6%, $p < .001$).

Further splitting up the data by age group and intervention shows that decoding is consistently above chance in all conditions (all $ps < .022$, uncorrected). Classifier performance for each intervention and age group is shown in figure S2. As reported in the main text (Results), no effects of intervention were found ($t(603) = -.211$, $p = .833$) and permutation tests confirmed these findings (test of true value against permutation distribution of 1000 differences between interventions given shuffled training labels, $p = .566$).

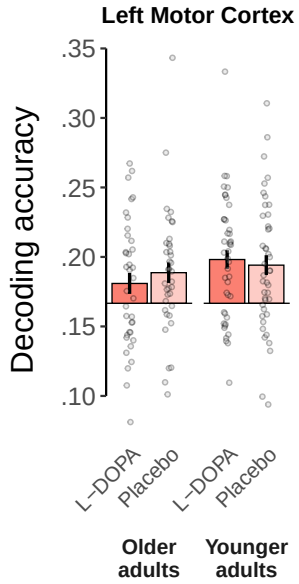

Figure S2: Classification accuracy of direction in the left motor cortex. Bars show average classification accuracy for each intervention and age group. Dots represent values of individual participants. Error bars show standard error of the mean.

3 Number of classifier examples between sessions and age groups

We first investigated systematic differences in the total number of classifier examples between age groups and sessions using a linear mixed effects model with a random intercept of participant. There was no significant effect of age group on the number of classifier examples ($\chi^2(1) = 1.335$, $p = .248$). The model showed a significant effect of session ($\chi^2(1) = 9.405$, $p = .002$), which described a lower number of events in the second session (on average 7.8 events difference) as revealed by post-hoc tests. This is likely to be caused by a training effect that the task might be solved more efficiently the second time resulting in less data due to a shorter navigation

time. More importantly, our analyses in the paper are based on the drug intervention, which was balanced across both sessions (counter-balanced intervention order: L-DOPA–Placebo or Placebo–L-DOPA). When running the same model with a fixed effect of intervention instead of session we found no difference in the number of events (mean number of events: 94.05 vs. 94.69 for Placebo and L-DOPA, respectively; $\chi^2(1) = .051$, $p = .822$). This model also did not display an effect of age group ($p = .248$). Furthermore, neither the model including the fixed effect of session, nor the model including the fixed effect of intervention showed a significant interaction with age group ($ps \geq .299$). When repeating the intervention analysis separately for each of the six directions only two of the six models showed marginal effects of age group. Because of the weak evidence for these effects and the high amount of comparisons made we did not interpret these findings as systematic differences in the number of classifier examples. Based on these findings, we are confident that differences in the number of classifier examples cannot explain our results.

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E Article III

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Influence of surprise on reinforcement learning in younger and older adults

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Abstract

Surprise is a key component of many learning experiences, and yet its precise computational role, and how it changes with age, remain debated. One major challenge is that surprise often occurs jointly with other variables, such as uncertainty, outcome magnitude and outcome probability. To assess how humans learn from surprising events, and whether aging affects this process, we studied choices while participants learned from stationary asymmetric outcome distributions, which decouple outcome magnitude and probability from uncertainty and surprise. A total of 102 participants (51 older, aged 50 – 73; 51 younger, 19 – 30 years) chose between three bandits, one of which had a bimodal outcome distribution. Behavioral analyses showed that both age-groups learned the average of the bimodal bandit less well, and performed decision errors consistent with heightened sensitivity to surprise, as measured by large absolute prediction errors. This effect was stronger in older adults. Computational models indicated that learning rates in younger as well as older adults were influenced by surprise, rather than uncertainty. Our findings bridge between behavioral economics research that has focused on how outcome probability affects simple choice in older adults, and reinforcement learning work that has investigated age differences in the effects of uncertainty in complex non-stationary environments. The reported age differences shed novel light on the factors that alter learning and choice in older age.

Significance Statement:

Keywords: aging; reinforcement learning; behavioral modeling; surprise; uncertainty

1 Introduction

Aging changes how humans learn and decide in ways that can affect important life choices, such as monetary or health decisions (Mather et al., 2012; Tymula, Rosenberg Belmaker, Ruderman, Glimcher, & Levy, 2013; Nassar et al., 2016; Eppinger, Hämmerer, & Li, 2011). Previous research has shown that aging impacts how different characteristics of a choice situation, such as risk (Mata, Josef, Samanez-Larkin, & Hertwig, 2011; Best & Charness, 2015), ambiguity (Tymula et al., 2013), uncertainty (Nassar et al., 2016), feedback (Eppinger, Schuck, Nystrom, & Cohen, 2013; Samanez-Larkin & Knutson, 2014; Schuck et al., 2018), or explicit knowledge (Curran, 1997) impact learning or decision making. One essential factor that could underlie these effects is how humans process outcomes that occur rarely and/or are 'extreme', i.e. differ significantly from more commonly encountered values. Seminal work on prospect theory (Kahneman & Tversky, 1979; Tversky & Kahneman, 1992) has for instance shown that college-aged adults overweight events with low probabilities during decision making, and perceive relatively less gains with larger outcomes, which could explain why people are often uncertainty-averse in the gain domain (Platt & Huettel, 2008). Differential processing of rare or extreme outcomes could also influence decision making informed by past events: memory tends to be better for values at the edges of distributions (Madan & Spetch, 2012; Madan, Ludvig, & Spetch, 2014; Ludvig, Madan, McMillan, Xu, & Spetch, 2018), and for events associated with less expected outcomes (Rouhani, Norman, & Niv, 2018).

Here, we study how aging affects the way in which we learn value maximizing choices from extreme versus more common outcomes. While the above mentioned research mostly focused on single choices made on the basis of descriptions, we focus on the process that lets humans learn how to decide from trial and error. Our theory is based on a reinforcement learning (RL) perspective (Sutton & Barto, 2018) that has yielded crucial insights into the behavioral and neural aspects of this learning process in the past (e.g., see Dayan & Daw, 2008). At the center of RL theory lies the concept of the prediction error, which reflects the relative deviation of an observed outcome from the current expectation for a given bandit/gamble. In its most basic formulation, RL theory says that the prediction error is used to update future expectations after an outcome has been observed by multiplying it with a constant

learning rate, $\alpha \in [0, 1]$. Hence, rather than focusing on absolute outcome magnitude, RL casts learning and decision making in terms of a *relative* quantity, i.e. the deviation from a given expectation. Prediction errors are also distinct from outcome probabilities. Although outcome probabilities and magnitude are correlated in uni-modal Gaussian distributions, this correlation is reduced or absent in long-tailed or bi-modal distributions, where for instance outcomes with a relatively small difference from the mean can occur equally or more rarely than outcomes of greater (relative) magnitude. Here we derive two quantities from the prediction error that relate to the above mentioned concepts of outcome magnitude, probability and uncertainty: the unsigned prediction error, that reflects participants surprise, and the trailing average of surprise, which reflects how much uncertainty participants experienced in the past (Hayden, Heilbronner, Pearson, & Platt, 2011; Nassar et al., 2016).

Previous work taking a RL perspective on aging has suggested that in particular uncertainty processing, but not surprise processing, is impaired in older adults (Nassar et al., 2016). This conclusion, however, was reached in the context of a complex choice situation in which participants had to track non-stationary bandits. Using such a task, Nassar et al., 2016 focused on how participants modulated learning rates in response to outcome deviations that reflected a true shift of the bandit mean versus merely a random deviation due to variability around each bandit's mean.

Although decision making in volatile environments is an interesting computational problem, many choices in everyday life are arguably simpler. We therefore considered a much simpler situation in which participants learned the means of stationary bandits. This setup allowed much simpler formulations of surprise and uncertainty that offer greater similarities to the work done on aging in behavioral economics (Mata et al., 2011; Pachur, Mata, & Hertwig, 2017) and require fewer assumptions about how the complex computational processes involved in learning about non-stationary environments are implemented in the brain (Behrens, Woolrich, Walton, & Rushworth, 2007; Nassar, Wilson, Heasly, & Gold, 2010). In order to differentiate surprise from previously studied concept of outcome magnitude and probability discussed above, we made use of two facts: (1) that surprise has a non-linear relation even to relative outcome magnitude and (2) that bi-modal outcome distributions decorrelate outcome magnitude and probability as mentioned above.

Following this logic, we developed a novel task that involves learning from stationary bimodal outcome distributions. We used this task to test two effects. On the one hand, inspired by work on age differences in probability weighting (Pachur et al., 2017), we stipulated that surprise could affect the learning rate with which participants update their expectations. Our simple assumption was that surprises would modulate learning rates *immediately*, i.e. affect the update on the very same trial that caused the surprise – akin to a process that gives more weight to a very surprising (although not rare) event. Although this idea is similar in spirit to proposals by e.g. Nassar et al., 2010, it is distinct from existing RL models in which learning rates reflect the agent's estimate of the volatility of the environment, which is is in turn based on variability of *past* outcomes (Pearce & Hall, 1980; Li, Schiller, Schoenbaum, Phelps, & Daw, 2011; Jepma et al., 2016; O'Reilly, 2013; Nassar et al., 2010). Since Pachur et al., 2017 have shown that in the gain domain older adults overweight low probability events more compared to younger adults, we expected that surprise-dependent learning rate modulation would be larger in the former. The second effect we sought to test was whether younger versus older participants differed in the amount of uncertainty/risk aversion in ways that goes above and beyond differences in surprise-dependent learning. Specifically, we assessed whether a recency-weighted average of past surprise magnitude changed bandit preferences independently of the experienced outcomes, and independently of any effects of surprise on learning rates. Previous research has indicated that age effects in uncertainty processing depend on the specific computational concept and task used to study them (Mata et al., 2011; Nassar et al., 2016; Pachur et al., 2017). Hence, we had no specific hypothesis if age differences in uncertainty would be found in our computational and task setting.

2 Materials and Methods

2.1 Participants

Participants were recruited using the crowdworking platform *Prolific* (`www.prolific.co`). We collected data of 64 YA (18-30 years, mean age 24.42) and 56 OA (50-73 years, mean age 57.18). Eighteen participants (13 YA, 5 OA) were excluded from all analyses due to insufficient task performance across both runs; 17 (12 YA, 5 OA) participants did not show

significant above-chance performance in the easiest task condition (using a binomial test against chance in low vs. high bandit trials, see below), and one young adult had a disproportionate amount of errors in guided choice trials compared to the rest of the sample (more than three SDs from mean of distribution). The effective sample of choice trials therefore consisted of 102 participants (51 YA, 51 OA).

To ensure high data quality in the analyses of the estimation trials, of which only 16 existed per run (see below), we applied additional exclusion criteria exclusively for these analyses. Specifically, data from runs in which a participant did not show any overall difference in estimates of the low versus high bandit, or did not show any variance in their estimates, were excluded. This resulted in the exclusion of 12 runs from 10 participants for indistinguishable low vs. high estimates (no sig. difference in paired t-test) and of 2 runs from one participant due to no variance in submitted answers. Estimation-based analyses therefore included data of 99 participants (49 YA, 50 OA), out of which 8 participants had only one remaining run.

The experiment lasted about 60 minutes and was renumerated with a baseline payment of 7.5 GBP plus a performance based bonus of up to 3 GBP (see below). All participants provided informed consent and the local ethical review board approved the study (approval number: N-2020-01).

2.2 Valued-based Learning Task

The task consisted of two runs of a value-based choice task. In each run participants learned about three different bandits that rewarded outcomes drawn from distributions with a low, medium or high mean (outcome range 1-100, details see below). We will refer to these bandits as the *low*, *mid*, and *high* bandit, respectively (see below for details, and Fig. 1B). Each bandit was indicated by a different Japanese Hiragana symbol (randomly assigned across participants), and participants had to learn about each bandits' value through trial and error. Points collected were translated into a monetary bonus of up to 3 GBP at the end of the experiment.

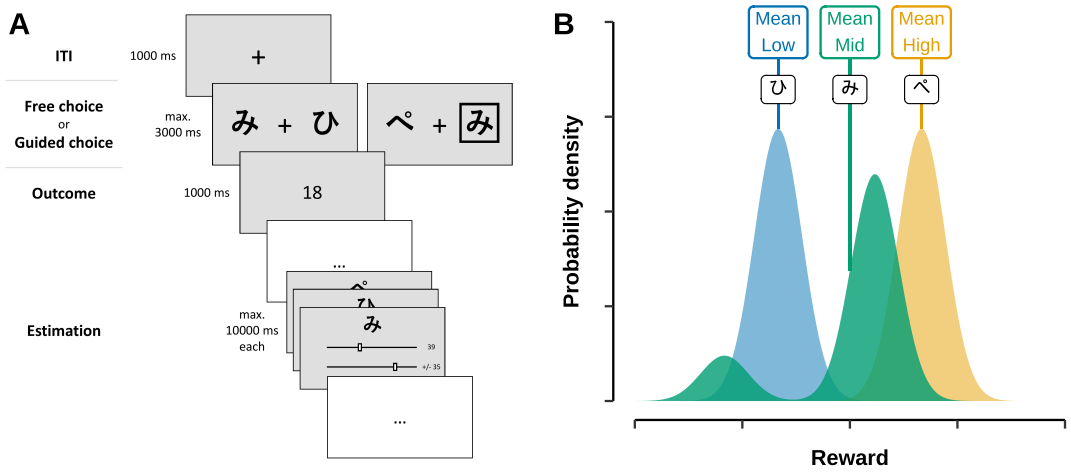

Figure 1: **A**: Schematic of task procedure. The first three steps show the procedure of a free choice or guided choice trial. After a brief inter trial interval of 1000 ms participants were confronted with a choice between two bandits. In free choice trials participants could freely choose either of both bandits. In guided choice trials participants were instructed to choose the framed option. After a choice was made the outcome of said choice was displayed for 1000 ms. Occasionally, participants had to complete estimation trials in which they had to estimate how many points they will get when choosing each bandit as well as the range in which the points may vary. **B**: Schematic of reward distributions. Each bandit was linked to one of three reward distributions: one with a low, medium, and high average reward. Means of subsequent distributions were equidistant (16.66). While the low and high distribution were Gaussian the mid distribution was bimodal with the two modes being 35 points apart. The smaller mode was always to the left of the greater mode and made up 20% of possible rewards. The absolute means of distributions varied between runs while the distance between distributions and distance between modes of the mid distribution never changed.

Reward distributions

To answer our main question about how participants learn from rare outcomes, we manipulated the reward distributions of the different bandits (see Fig. 1B). Rewards of the low and high average bandit were drawn from regular Gaussian distributions with a standard deviation of 5.55 points. The means of both Gaussians were fixed within each run and always chosen in a way that they were 33.33 points apart. The rewards of the mid bandit followed a bimodal mixture distribution composed of two Gaussians (each sd = 5.55 points): a main mode (80% of outcomes) and a smaller mode (20% of outcomes) with a distance of 35 points. The total mean of the mid bandit was equidistant from the means of the low and high bandits, 16.66 points away. Notably, although the overall mean of the mid bandit was higher than low bandit, the smaller mode of the mid bandit was lower than the low bandit. This asymmetrical outcome distribution of the mid bandit was central to the idea of the task: while the medium bandit on average delivered higher outcomes than the low bandit, it sometimes produced an unusually low outcome in 20% of choices that was sampled from the lower mode of the distribution. We therefore expected that over- or underweighting of

surprising outcomes would specifically bias participants' decisions between and estimations of the low and medium bandit.

At the start of a the second run a separate set of three bandits was introduced. The absolute means of each distribution changed between runs by up to 14.8 points, while their relative structure (distance between means, distribution shapes) remained the same. Participants were made aware that outcomes and symbols were changed at the start of the new run. Rewards were constrained to lie between 0 and 100.

Free/Guided Choice trials

On each choice trial participants had to decide between two bandits, ensuring that all pairwise bandit combinations appeared with equal frequency within each run. In free choice trials (192/240 trials per run), participants could freely chose between the offered bandits within a maximum of 3000 ms. After a choice, the outcome was displayed for 1000 ms, followed by a fixation cross (1000 ms) to allow for preparation for the next trial. Not responding within the maximum of 3000 ms resulted in 0 points and a hint to respond faster. In guided choice trials (48/240 trials per run) participants had to chose the bandit that was marked with a frame, while all other task aspects were kept the same, and collected points were awarded as usual. Choice trials are illustrated in Figure 1A, top.

Estimation trials

Each run also included 16 estimation trials in which participants were asked to estimate how many points would be obtained from a bandit, and to which degree the outcomes may vary (Fig. 1A, bottom). Estimates were collected for all three bandits and had to be provided by adjusting two independent sliders that ranged between 0 and 100 for the average estimate and from ± 0 to ± 50 for the range estimate (with a step-size of 1, and a maximum decision time of 10 seconds). No feedback about their estimation was provided and participant could not earn points for accurate estimations. Estimation trials occurred at pseudo-random times within the run, assuring that there were no estimation trials within the first 10 choice trials, all estimation trials were at least 10 choice trials apart (on average, estimation trials were separated by 14.98 choice trials), and 4-5 estimation trials occurred immediately after a

guided choice trial of the mid bandit that produced an extreme, low outcome drawn from the smaller mode of the bimodal distribution (see below).

2.3 Statistical analyses

Behavioral analyses were done using linear mixed effects (LME) models with fixed effects of interest, such as bandit comparison (which bandits are compared, 3 levels, low-mid, mid-high, low-high), run number (2 levels), and age group (2 levels: OA vs. YA). Models also included a random effect (intercept) of participant. These models investigated overall performance (percentage of correct free choice trials) and choice speed (reaction times; all reaction times were collected in milliseconds and log-transformed before entering any analyses). To investigate the effect of large PE outcomes specifically, we analyzed free choices in low-mid trials before and after participants encountered a rare outcome of the mid bandit (on average n = 4.71 and n = 4.44 choices per run/participant, respectively). This was compared to choices in low-mid trials following less surprising outcomes from the 20th to 40th percentile of the distribution. The model for this analysis included a fixed effect of position relative to a rare outcome (pre vs. post), in addition to the fixed and random factors mentioned above, i.e. run and age group and participant, respectively.

Statistical inference was done through χ^2 likelihood ratio tests to determine whether the inclusion of the a particular fixed effect in the model provided a significantly better fit (R package `lme4`, Bates, Mächler, Bolker, & Walker, 2015). Posthoc test were done using the `emmeans` package for R (Lenth, 2021) and were corrected for multiple comparisons applying Šidák correction.

Analyses of estimation trials

To check if estimates of each bandit deviated from their true average outcome estimates were compared to the running mean of collected outcomes of each bandit. Differences between a bandit's true average and participants' estimates were calculated to provide a measure of under- or over-estimation. Since learning in the initial trials will cause the estimated averages to fluctuate (in ways that could depend on participants unknown a-priori expectations of average outcomes), we considered only the second half of estimation trials for further analysis.

Over- or underestimations were assessed using one-sample t-tests separately for each bandit and age group. P values were Bonferroni-Holm corrected.

We also compared the difference in estimates of two bandits in regard to the their objective running average difference. Because our main hypothesis concerned biases in the mid bandit, we focused on the estimated differences between the low and mid bandits, and mid and high bandits. Subtracting the estimated differences from the corresponding objective differences yielded a measure of distortion in perceived distance between bandits for each comparison, whereby values lower than zero represent an underestimation of distance. This measure of distortion was analyzed using a LME model with fixed effects of age group, run, and available options (low-mid vs. mid-high) as well as a random effect of participant.

2.4 Computational Models of Surprise and Uncertainty

In order to gain insights into the dynamics of learning, and specifically into how uncertainty and surprise influence behavior, we applied four different RL models to participants' choice data. All models were based on a delta-rule updating mechanisms that yielded a recency-weighted value estimate of each bandit, but differed with respect to the assumptions about the learning rate and the influence of uncertainty on choice. An illustration of the models can be found in Fig. 2.

Rescorla Wagner Model As a baseline model we used a standard *Rescorla-Wagner* model (*RW* model, Wagner, Logan, & Haberlandt, 1968; Rescorla, 1968), in which the value of each bandit is the recency-weighted average of associated rewards, and is calculated iteratively as follows:

$$\begin{aligned} V_{k,t+1} &= V_{k,t} + \alpha\,(R_{k,t} - V_{k,t}) \\ &= V_{k,t} + \alpha\,\mathrm{PE}, \end{aligned} \tag{1}$$

where $V_{k,t}$ denotes the value estimate of bandit k on trial t, and $R_{k,t}$ is the corresponding reward obtained at time t after choosing k. The difference between the expected and obtained value is referred to as the prediction error (PE, here $R_{k,t} - V_{k,t}$), and $\alpha \in [0, 1]$ is a learning rate fitted as a free parameter. The probability to chose bandit k over bandit l, given the

model values, was computed using a logistic regression:

$$p(k|V_{,t}) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 V_{l,t} + \beta_2 V_{k,t})}} = \sigma\left(\beta_0 + \beta_1 V_{l,t} + \beta_2 V_{k,t}\right) \quad , \tag{2}$$

where $\sigma(\cdot)$ indicates the logistic function and the parameters β_0, β_1 and β_2 reflect the intercept and the influence of the values of bandits k and l, respectively, determined using maximum likelihood estimation, as implemented in function `glm` in R (R stats; Team, 2021).

Uncertainty Model To test whether recently experienced uncertainty also influenced choices (in addition to values), we constructed the *Uncertainty* model. We adopted the hybrid RW/PH model by Li et al. (2011) to keep track of the recency-weighted uncertainty of each bandit:

$$U_{k,t} \; = \; (1 - \pi)\, U_{k,t-1} \; + \; \pi \, |\mathrm{PE}_t| \tag{3}$$

The free parameter $\pi \in [0, 1]$ determines the degree of recency-weighting of prediction errors that form the agent's current uncertainty estimate. Values close to 1 mean that only the most recent errors are considered while values closer to 0 mean that the agent considers long history of errors.

Note that the prediction error associated with a particular bandit only gets updated when that bandit was sampled, while the trial counter t refers to all trials. In the *Uncertainty* model, the uncertainties U were then added to the logistic regression:

$$p(k) \; = \; \sigma\left(\beta_0 + \beta_1 V_{l,t} + \beta_2 V_{k,t} + \beta_3 U_{l,t} + \beta_4 U_{k,t}\right) \tag{4}$$

Surprise Model Our second main interest was to ask whether large absolute prediction errors, i.e. surprise, influenced learning rates, rather then affecting choices directly as in the *Uncertainty* model. Specifically, we asked whether observing extreme outcomes would influence participants' learning rate, compared to observing less surprising outcomes. To this end, we modified the learning rule given in Eqn. 1 to include a variable learning rate

α^*, which itself was a logistic function of the (scaled) prediction error:

$$\begin{aligned} \alpha^* &= l + \frac{2}{1 + \widehat{\mathrm{PE}}^{-s}} (u - l) \\ V_{k,t+1} &= V_{k,t} + \alpha^* \, \mathrm{PE}_t \\ &= V_{k,t} + \left(l + \frac{2}{1 + \widehat{\mathrm{PE}}^{-s}} (u - l) \right) \mathrm{PE}_t \end{aligned} \tag{5}$$

Hence, instead of a single learning rate α, this model required three fitted parameters, a lower bound $l \in [0, 1]$, a upper bound $u \in [0, 1]$ and a slope, $s \in [-20, 20]$. These parameters regulated the influence of prediction error dependent surprise, specifying the alpha level when the PE was 0 (l), when the PE was maximal (u), as well as the slope (s) between these two extremes indicating at which levels of surprise learning rates are adjusted (see Fig. 2C). Note that in case $l > u$ the function specifies a decreasing function and v.v. if $u > l$, and the slope parameter allowed to accommodate a wide range of relationships between the learning rate and the predictions error. $\widehat{\mathrm{PE}}$ reflects an absolute PE term defined as

$$\widehat{\mathrm{PE}} = \frac{2}{1 + e^{-0.1|\,\mathrm{PE}|}} - 1 \tag{6}$$

and scaled by the maximal possible PE value of 60. The updating detailed in Eqn. 5 altered the estimated values. These values were then used to predict choices as in the baseline model (Eqn. 2), yielding the *Surprise* model.

Surprise+Uncertainty Model Finally, we tested for the combined influence of surprise and uncertainty on choices by entering the new values as estimated by the surprise model jointly with the uncertainties into the logistic regression (as in Eqn. 4) to explain choices.

2.5 Model fitting

Parameter fitting consisted of fitting the β coefficients of the logistic choice model, and the parameter(s) of the learning rate function and, if included, the uncertainty function. Fitting minimized each models' choice likelihood using a nested approach akin to a coordinate descent approach (see Hall-McMaster, Dayan, & Schuck, 2021). Specifically, the

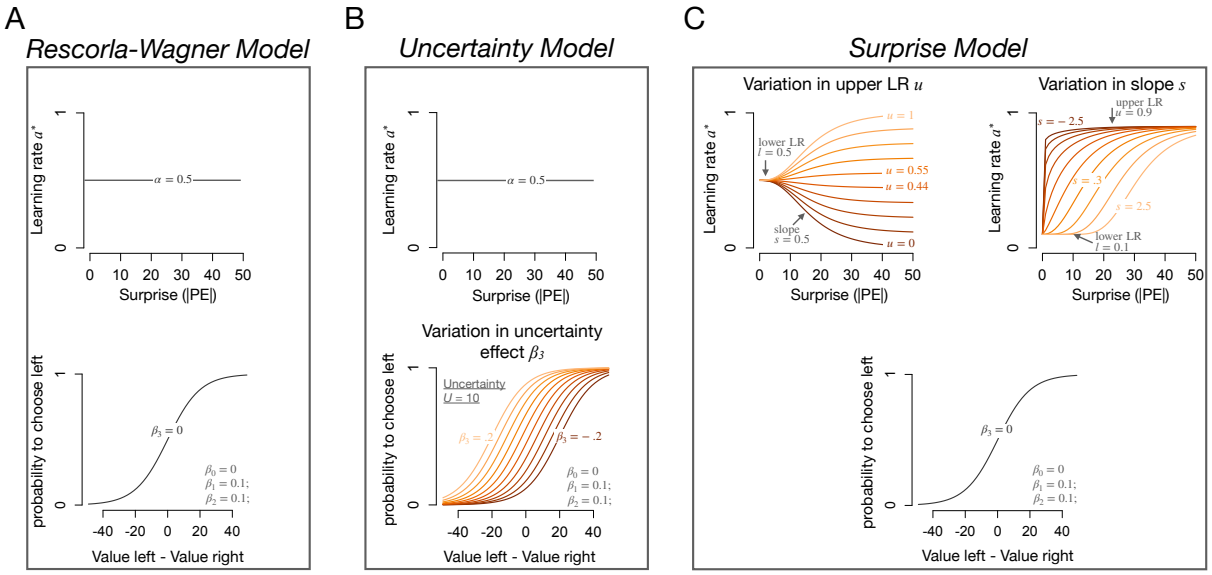

Figure 2: Illustration of computational models. For each model depicted on top is the sensitivity of trial-wise instantaneous updates (learning rate) to the surprise (i.e., unsigned prediction error) associated with an outcome of a bandit choice. On the bottom via β_3 is shown the influence of the left bandit's uncertainty U (estimated by the agent) on choice probabilities of the two candidate bandits (see Eq. 2). **A**: *Rescorla-Wagner* model in which updates and choices are insensitive to both, surprise and uncertainty. **B**: *Uncertainty* model in which updates are insensitive to surprise but bandit choices are influenced by uncertainty. Note, how uncertainty in the left bandit can heighten ($\beta_3 > 0$) or lower the probability of choosing the left bandit ($\beta_3 < 0$). Uncertainty estimates of each bandit are fixed to $U = 10$ for the illustration but in the model depend on a free parameter π (see Eq. 3). The influence of the right bandit's uncertainty (β_4) is left out for simplicity. **C**: *Surprise* model which is insensitive to bandit uncertainty, but in which trial-wise updates are influenced by surprise in dependence of the parameters l, s, and u (see Eq. 5). As depicted on top, high levels of surprise can either increase ($u > l$) or decrease the learning rate on a given trial ($u < l$). Lower values of the slope parameter s indicate that updating is adjusted already for lower levels of surprise. Not depicted is the *Uncertainty+Surprise* model which combines the principles of **B** and **C**.

parameters of the learning rate function (simply α in the *RW* and *Uncertainty* models, but [l, u, s] in the *Surprise* models) were set in an outer loop using non-linear search method (`NLOPT_GN_DIRECT_L`, Gablonsky & Kelley, 2001) implemented in the `nloptr` package (Johnson, 2020) in R. The β coefficients were then set using maximum likelihood estimation in an inner loop, and the resulting choice likelihood was used to inform the non-linear search for the outer parameters. To capture the behavioral effect in response to the one-sided bimodal distribution of the Mid bandit models were fit to participants' free choices in low-mid bandit comparisons. Furthermore, guided-choice and estimation trials were not used during the minimization process. Parameters were constrained to lie in the intervals given above. To avoid overfitting, model fits were compared using corrected Akaike Information Criterion (AICc, Cavanaugh, 1997) scores, a metric that more strongly considers the amount of trials used.

3 Results

3.1 Behavioral analysis

We first asked whether participants learned to make reward-maximizing choices, and whether the proportion of correct responses in free choice trials differed between available options.

A corresponding LME model of correct choice probabilities revealed a main effect of run ($\chi^2(1) = 12.061, p = .001$) reflecting a performance increase across runs (post hoc test: $t(500) = -3.473, p < .001$). Independent of this general improvement the LME model also showed a main effect of bandit comparison (low-mid vs. mid-high vs. low-high, $\chi^2(2) = 155.332, p < .001$). More specifically, participants performed best on low-high trials with 92.6% correct choices ($t(500) < -4.962, p < .001$, copared to low-mid and mid-high). On low-mid trials participants chose correctly in 79.2% of trials. Despite the bandit means being equidistant in low-mid and mid-high trials, participants were significantly more accurate for mid-high comparisons (87.2%, $t(500) = 7.420, p < .001$), reflecting the asymmetric shape of the mid reward distribution. Note that any value compression for numerically higher outcomes, as commonly observed in perception (Arnaud, Hubbard, Dehaene, & Sackur, 2010; Dehaene & Marques, 2002), should have the opposite effect, since 30 and 50 (low-mid trials) should be relatively easier to distinguish than 50 and 70 (mid-high trials).

The model revealed no significant effect of age group ($\chi^2(1) = 3.392, p = .066$) or age group × bandit comparison interaction ($\chi^2(2) = 2.380, p = .304$). Since the data of the OA group included two outliers (see Fig. 3D), we investigated the age group × bandit comparison interaction effect using a robust regression. A direct comparison of the difference between low-mid vs. mid-high trials between OA and YA indicated a significant difference: compared to younger adults, older participants had a greater performance decrease in low-mid relative to mid-high trials (robust regression with bisquare weights, $t(100) = -2.735$, $p = .010$)

A similar pattern was found in participant's RTs. An LME model of log-transformed RTs also showed a main effect of bandit comparison ($\chi^2(2) = 457.891$, $p < .001$). The decreased performance on low-mid trials reported above was also associated with lower RTs compared to mid-high trials ($t(500) = 16.121$, $p < .001$), while the fastest reactions were shown in low-high trials (mid-high vs. low-high: $t(500) = 4.126$, $p < .001$). Moreover, the

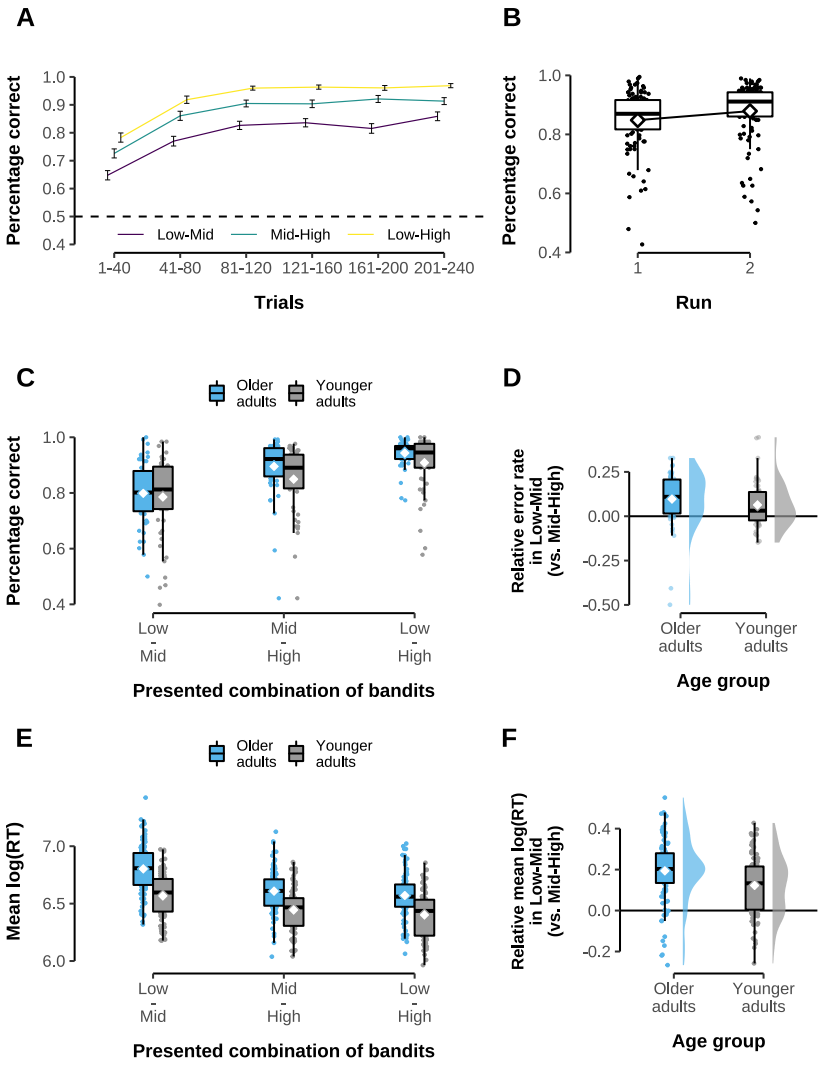

Figure 3: **A**: Performance over time within run. Plotted are progressing trials in bins of 40 on the x-axis with the percentage of correct answers (i.e. choosing bandit with higher average outcome) in free-choice trials on the y-axis. The progression is shown and colored separately for each of the three possible bandit combinations that could appear in any trial (low-mid, mid-high, low-high). Dashed line indicates chance-level performance. Error bars show standard error of the mean. **B**: Across-run difference in overall task performance, irrespective of presented bandit combination. Participant-specific values are given by black dots. **C & D**: On left: Performance for each possible combination of bandits (low-mid, mid-high, low-high) by age group, averaged across both runs. Older adults are shown in blue, younger adults in grey. Choosing the bandit with higher average outcome was considered a correct choice. Individual values are shown by colored dots, group averages by white diamonds. On right: Direct comparison of correct answers in the low-mid vs. mid-high trials for each age group. Shown are within-participant differences between those percentages correct in low-mid and mid-high trials depicted in panel C. Values above the zero line indicate more errors in low-mid trials compared to mid-high trials. Individual values are given by colored dots, group means by white diamonds. Note, that we specifically compare these two combinations as the average reward of the Mid bandit was equidistant to those of the Low and High bandit. **E & F**: On left: Comparison of reaction times (RT) in free-choice trials across all three possible bandit combinations by age group. Older adults in blue, younger adults in grey. The y-axis shows the mean over log-transformed RTs averaged across both runs. Higher values indicate longer RTs (slower responses). Means and individual values depicted as in C and D. On right: Direct comparison of RTs in low-mid vs. mid-high trials shown in panel E for each age group. Shown are within-participant differences in mean log-transformed RTs between the low-mid and mid-high bandit combinations. Values above the zero line indicate longer RTs in low-mid trials. Means and individual values depicted as in C and D.

same LME model also showed a main effect of age group ($\chi^2(1) = 31.356$, $p < .001$) as well as an age group × bandit comparison interaction ($\chi^2(2) = 16.360$, $p < .001$). This reflected that OAs in general reacted slower than YAs ($t(100) = 5.600$, $p < .001$). Importantly, OAs reacted slower than YA in low-mid trials (difference = .236, $t(123) = 6.589$, $p < .001$). Captured in the significant age group × bandit comparison interaction was the fact that age differences in RTs were more pronounced in low-mid trials compared to other bandit comparisons (difference = .164 and .170, $t(123) \geq 4.593$, $ps < .001$ for mid-high and low-high, respectively).

Immediate influence of extreme outcomes

To better understand how participants were influenced by surprising outcomes, we investigated the immediate effect of outcomes that elicited large absolute PEs in the low-mid bandit on subsequent choices. Specifically, we compared the proportion of mid bandit choices in low-mid trials immediately before vs. immediately after a surprising outcome (LME model with effects for before vs. after and age group, see Methods). This analysis revealed that across both age groups the choices of the mid bandit following large absolute PEs were decreased (main effect pre- vs. post: $\chi^2(1) = 28.160$, $p < .001$; 82.2% vs. 70.1%, $t(299) > 5.314$, $p < .001$). However, as suggested by a significant position × age group interaction ($\chi^2(1) = 5.844$, $p = .016$) the adaption of choices was only significant in OA (pre-post difference: 17.6%; $t(299) = 5.458$, $p < .001$) while YA only trended towards a similar effect (pre-post difference: 6.6%; $t(299) = 2.052$, $p = .080$, Šidák corrected). Results are displayed in Fig. 4. To see if this was a general reaction towards below-average outcomes of the mid bandit, we repeated the same analysis for low-mid trials immediately before and after less extreme outcomes (mid-bandit outcomes between the 20th and 40th percentile). No effects of either pre vs. post or age group were found ($\chi^2(1) = .541$, $p = .462$ and $\chi^2(1) = .968$, $p = .975$, respectively). The model of the immediate effect of surprising outcomes also indicated a significant main effect of run ($\chi^2(1) = 12.438$, $p < .001$) that reflected a general increase in mid bandit choices in low-mid trials in the second run ($t(299) = -3.530$, $p < .001$).

Importantly, we found no evidence of a more general age group difference in mid-bandit

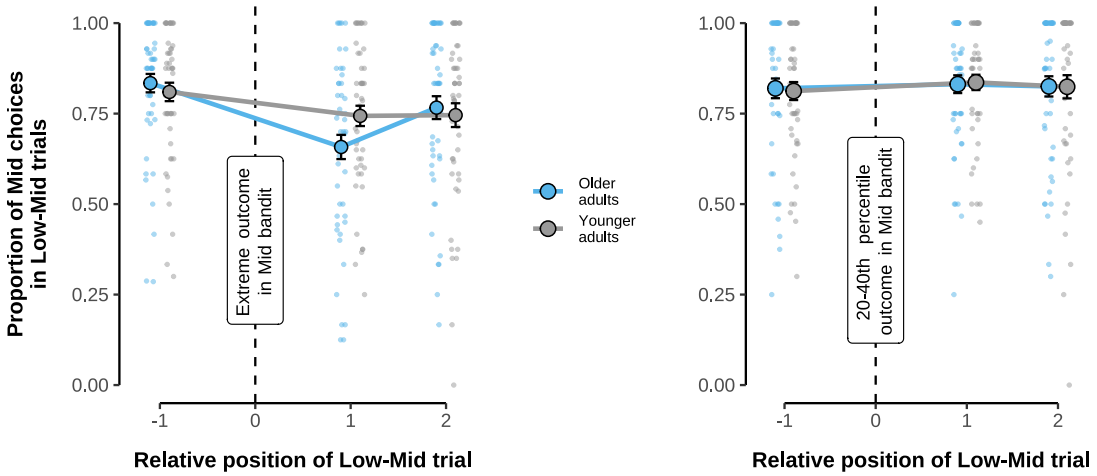

Figure 4: Influence of extreme or regular low outcomes on following low-mid comparison choices by age group. Older adults in blue, younger adults in grey. Small dots give individual values, large dots depict group means with standard error of the mean shown by error bars. On left: Influence of extremely low outcomes in the mid bandit on choices in immediate low-mid trials. Shown on the x-axis are positions of low-mid trials relative to the extreme outcome where -1 and 1 denote low-mid trials happening immediately before and after the extreme outcome, respectively. Indicated by the zero is the trial which produced an extreme outcome in the mid bandit (not necessarily a low-mid trial). The y-axis shows the proportion of mid bandit choices in the respective group of trials given by the x-axis. A lower value on the y-axis indicates that the proportion of low bandit choices increased. On the right: Influence of moderately low outcomes (20th to 40th percentile) in the mid bandit on choices in immediate low-mid trials. See description of left plot for details.

choices (LME model main effect of age group: $\chi^2(1) = 1.363$, $p = .243$; no effect of run, $\chi^2(1) = 0.154$, $p = .694$). Hence, the above effect cannot be explained by age group differences in risk aversion, which would result in overall reduced choices of the mid bandit due to it's more extreme outcome distribution.

Value Estimates

We next checked for systematic biases in estimation trials, rather than choice behavior, and asked how accurate participants' estimates were relative to the ground truth running average of each bandit. To avoid effects of non-stationarity during early learning, analyses were conducted on the second half of each run. Comparing the across-run average estimates vs. ground truth separately for each bandit and age group did not indicate any significant difference (YA: $ps \geq .111$, OA: $ps \geq .625$; the largest difference found indicated a non-significant underestimation of the high bandit in YA $t(48) = -2.437$, $p = .111$, Bonferroni-Holm corrected). This indicates that participants estimates were relatively accurate on average.

Importantly, we next asked how the estimated difference between bandits (i.e. low bandit

minus mid bandit or mid bandit minus high bandit) related to their true difference (difference of running means). A LME model of the mis-estimation of bandit differences revealed a main effect of bandit pair ($\chi^2(1) = 34.536$, $p < .001$), and an interaction of bandit pair with age group ($\chi^2(1) = 8.280, p = .004$), see Fig. 5. On average, both age groups perceived the low and mid bandit to be closer together compared to their true distance (OA underestimated the difference by -3.68 points, YA by -1.93 points). Post-hoc tests revealed that the underestimation of the low-mid difference relative to the mid-high difference was significantly larger in older compared to younger adults ($t(277) = 2.051, p = .041$).

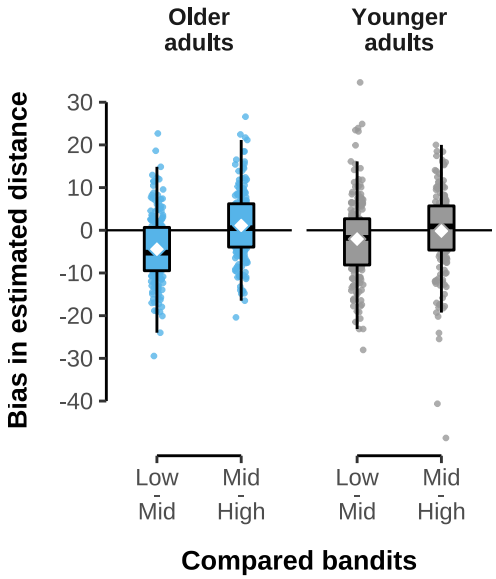

Figure 5: Bias between perceived and true distance of two neighboring bandits for both age groups. Older adults in blue, younger adults in grey. Individual values shown by colored dots and means shown by white diamonds. On the x-axis both pairs of equidistant, neighboring bandits (low-mid and mid-high). The y-axis shows discrepancy between perceived and true distance of the two compared bandits. Perceived distance of two bandits was given by the difference between participants' estimates of the two compared bandits. True bandit distance was given by the difference between the running means of the two compared bandits. Subtracting the true distance form the perceived distance allows to quantify a bias in estimated distances. Values lower than zero indicate an underestimation of bandit distance, perceiving them closer in space than their true distance.

3.2 Computational modelling

The above analysis indicated that participants performed worse in low-mid trials compared to mid-high trials, and underestimated the same bandit differences. This effect was particularly pronounced for older adults, who altered their choice preferences immediately following large PE events caused by the mid-bandit's bi-modal outcome distribution, and underestimated the true value of the mid bandit more so than younger adults.

Using computational models, we asked whether the differences in low-mid trials could be explained by either an influence of uncertainty, surprise or both. We modelled participants choices in low-mid trials using the four models specified in the Methods section. A *Rescorla-Wagner* model that assumes a constant learning rate and no effects of uncertainty or surprise (Fig. 2A), served as a baseline. The *Uncertainty* model (Fig. 2B) tested whether subjects' choices were influenced by the unsigned magnitude of past prediction errors, i.e. whether they showed less or more preference for bandits that were associated with high/low uncertainty in the past. The alternative *Surprise* model (Fig. 2C) focused on the value learning process itself, and assumed that values could be updated with either a larger or smaller learning rate following each outcome. Finally, a combined *Uncertainty+Surprise* model encapsulated both mechanisms. The models are described in more detail in the Methods and are illustrated in Figure 2.

Logistic regression analyses indicated that the values estimated by the basic *RW* model influenced participants' choices. The probability of choosing the left bandit was positively influenced by the value of the left bandit in older as well as younger adults (avg. β younger: 0.16 [CI: 0.12 - 0.20], $t(50) = 7.92$, $p < .001$; older: $\beta = 0.19$ [0.15-0.22], $t(50) = 10.37$, $p < .001$). The reverse was true for the right bandit, i.e. we found negative betas of the right value in younger as well as older adults, both $t(50) < -8.88$, $p < .001$, as expected. The betas of the left and right bandit values correlated with the average percent of correct choices in low-mid bandit comparisons at $r = .26$ ($t(100) = 2.71$, $p = .016$) and $r = -.22$ ($t(100) = -2.24$, $p = .027$, Bonferroni-Holm corrected), respectively. Hence, participants performed the task in a manner generally consistent with reinforcement learning models.

Notably, however, the *RW* model did not offer the best fit to participants' choices. Participant-wise AICc comparisons were used to identify the winning model within each participant (see Fig. 6A). The most frequently winning model across all participants was the *Surprise* model (35 participants vs. 27, 27, 13, for the *RW*, *Uncertainty*, and *Uncertainty+Surprise* models, respectively). As shown in Figure 6B, this was was also reflected in a high protected exceedance probability for this model (91.8 %; via R package `bmsR`, Lisi, 2022; 10^5 samples; see Stephan, Penny, Daunizeau, Moran, & Friston, 2009). A χ^2-test did not find any significant difference across the four models and the age groups ($\chi^2(3) = 1.09$,

$p = .780$). Analyzing the parametric differences in AICc scores, the *Surprise* Model had significantly lower AICc scores compared to the baseline *RW* model in both age groups (OA: $t(50) = -3.41$, $p = .007$, YA: $t(50) = -3.50$, $p = .006$) while this was not the case for the other models ($t(50) > -2.05$, $ps \geq .165$, Bonferroni-Holm corrected; see Fig. 6C).

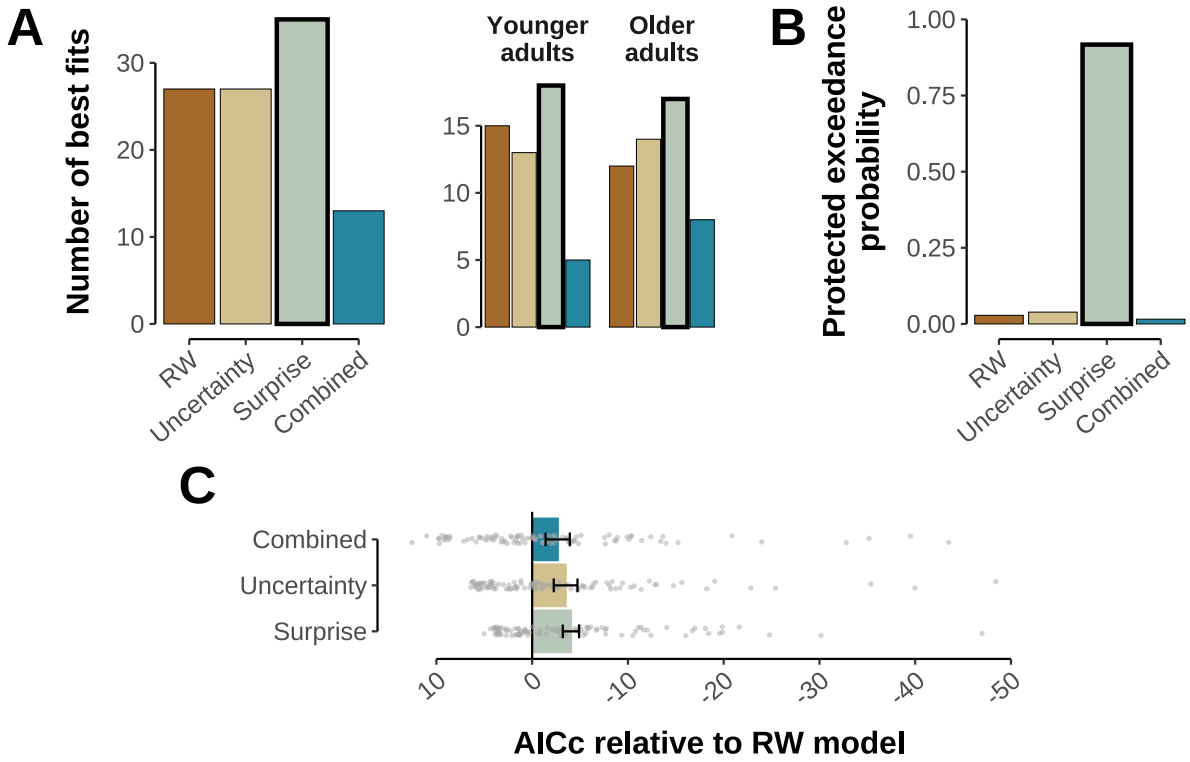

Figure 6: Model comparison. **A**: Number of participants in which each model offered the best fit shown across (left) and within age groups (right). The winning model was determined by a within-participant comparison of AICc scores in which the best fit was given by the lowest AICc score. **B**: Protected exceedance probability across all four candidate models and across both age groups. See Stephan et al. (2009) for details. **C**: Difference of AICc scores between candidate models and *RW* model ($\text{AICc}_i - \text{AICc}_{RW}$). Lower values indicate a better fit compared to the *RW* model. Dots represent individual values, while bars show mean AICc scores across both age groups. Error bars indicate standard error of the mean. Note, that in order to display the plot in a reasonable scale two outliers (large negative values, one in *Uncertainty*, one in *Combined* model) were removed from the plot. Mean and standard error of the mean still include all data points.

We therefore focused our following analyses on the *Surprise* model. Descriptive statistics of all model parameters as well as their relationship can be found in Figure 7A. First, we validated the model by relating participants' average performance on low-mid bandit comparisons to the β_1 and β_2 parameters, reflecting the influence of estimated bandit value on choices. Both parameters were significantly correlated with performance across age groups (β_1: $r = -.26$, $t(100) = -2.72$, $p = .015$; β_2: $r = .25$, $t(100) = 2.64$, $p = .015$, Bonferroni-Holm corrected). We then investigated the parameters related to the surprise effect on learning rate (l, u, and s; see Equation 5). Individual learning rates as a function of experi-

enced prediction errors for both age groups are shown in Figure 7B. Our previous behavioral analysis suggested OAs consider more surprising prediction errors more strongly in immediately following decisions (see Fig. 4). The different weighting of surprising prediction errors is captured in the relationship between the u and l parameters. Positive values ($u-l > 0$) reflect relatively faster learning (i.e., higher learning rate α) from large prediction errors while negative values ($u - l \leq 0$) reflect relatively faster learning from small PEs. To investigate age differences in the differential influence of surprising prediction errors, participants were split in two groups based on relative values of $u - l$. A χ^2-test did not indicate any significant difference in age groups and the relative number of participants that showed stronger or weaker influence of surprise ($\chi^2(1) = .66$, $p = .415$, see Fig. 7C). When investigating $u - l$ values parametrically, YAs trended towards higher learning rates for low surprise levels ($u - l = -0.17$, $t(50) = -2.19$, $p = .066$) while OAs did not show systematic differences ($u-l = -.05$, $t(50) = -0.78$, $p = .44$, one-sided t-test against 0, Bonferroni-Holm corrected). Comparing $u - l$ values between both age groups directly, however, did not reveal any age differences ($t(98.72) = -1.11$, $p = .268$). Investigating the slope parameter s yielded similar results and did not show any differences between age groups ($t(99.90) = .01$, $p = .993$). Finally, we investigated if the immediate effect of surprising mid bandit outcomes on low-mid bandit choices found in our behavioral analysis (see Fig. 4) was related to parametric $u - l$ differences. A linear model of the behavioral effect including the predictors age group and $u - l$ difference was marginally significant ($R^2_{adj.} = .044$, $F(3, 98) = 2.55$, $p = .060$). Importantly, however, $u - l$ differences had no predictive power over the behavioral effect ($t(98) = -.11$, $p = .913$) and the linear model's significance was driven by the significant terms of intercept and age group ($ps \leq .022$), as to be expected from the behavioral analysis.

Taken together, the computational modeling results suggest that participants' choices in low-mid bandit comparisons were mainly driven by surprise, as opposed to uncertainty or a combination of both mechanisms. This was shown by the best fit of the *Surprise* model. However, analyses of the *Surprise* model's parameters did not show any age differences related to the influence of surprising outcomes in low-mid trials evident in the behavioral analyses.

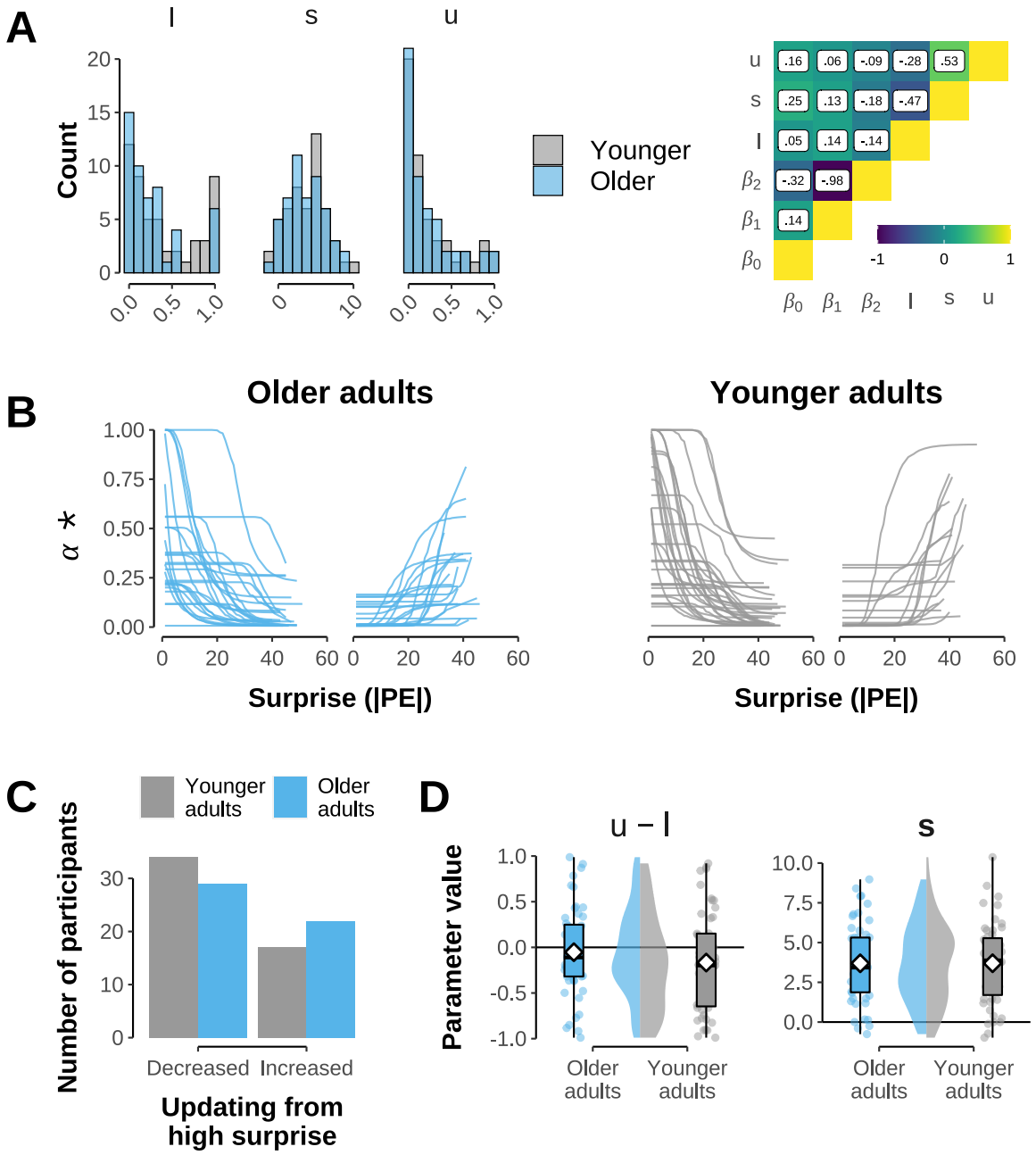

Figure 7: Analysis of *Surprise* model. **A**: Distribution and correlation between *Surprise* model parameters. On left: Histogram of model parameters l, s, and u involved in instantaneously adjusting learning rate as a function of surprise (i.e., unsigned prediction error; see Eq. 5) for younger and older adults. On right: Correlation matrix between all model parameters. Brighter colors show stronger positive correlation, darker colors stronger negative correlation. In each cell is shown the Pearson correlation between the respective parameters. **B**: Individual relationships between surprise about outcome (i.e., unsigned prediction error) and trial-specific learning rate $\alpha*$ as specified by the model parameters l, s, and u (see Eq. 5). Depicted separately within each age group are participants whose updating for high levels of surprise is *decreased* ($u - l < 0$, left) or *increased* ($u - l > 0$, right). **C**: Number of participants within each age group showing decreased ($u - l < 0$) or increased ($u - l > 0$) updating from higher levels of surprise. **D**: Age group comparison for parameters specifying differential updating from surprising outcomes. On left: Difference between u and l parameter. Values above zero indicate increased updating from surprising outcomes. Dots show individual values, diamonds show group-specific mean. Depicted in the middle are density plots of the respective age group's parameter distribution. On right: Slope parameter s. Depiction identical to left plot.

4 Discussion

In this study we investigated over- and underweighting of surprising outcomes during reinforcement learning, and asked whether age differences exists in this process. Our main hypothesis was that older adults show greater sensitivity to outcomes that elicit large prediction errors compared to younger adults. To this end, we analyzed behavior of 51 younger and 51 older participants in a multi-armed bandit task featuring two bandits with a Gaussian reward distribution of low and high mean, and one bandit with a asymmetric, bi-modal reward distribution of intermediate value. The asymmetric nature of the mid bandit's reward distribution was designed as such that overweighting of surprising outcomes during learning should result in non-optimal choices when comparing the mid-value (i.e., bimodal) bandit to the low-value bandit. We found that behavioral accuracy in low-mid bandit choices was significantly lower compared to mid-high trials despite the fact that both bandit pairs exhibited the same difference in their mean outcome. This suggests that surprising outcomes are overweighted, relative to ordinary outcomes. This effect was also mirrored in explicit value ratings, in which both age groups underestimated the difference in average rewards of the low and mid bandit, and older adults (OA) showed a stronger tendency to do so. An analysis of detailed choice time courses also found that extreme outcomes had a stronger influence on consecutive choices in OA compared to younger adults (YA). To explain these findings more formally, we compared four RL models that allowed us to address if participants' choices in low-mid bandit comparisons were driven by either uncertainty, differential updating from surprising outcomes, or a combination of both. The *Surprise* model offered the best explanation of participants' decisions overall. Although the *Surprise* model allowed a wide range of relationships between trial-wise learning rates and outcome surprise, the model's parameters did not reflect the age differences evident in the behavioral analyses.

Our results are consistent with findings that OA show stronger overweighting of low probability events when confronted with gambles in the gain and mixed domain (Pachur et al., 2017). Inspired by cumulative prospect theory (Tversky & Kahneman, 1992) and risky decision making paradigms (Mata et al., 2011), Pachur et al. (2017) asked participants to choose between two two-outcome monetary lotteries. Their core finding was that older adults overestimated the probability of rare events more than younger adults, i.e. that

the probability weighting function, which translates objective outcomes probabilities into subjective decision weights, was distorted more strongly in older adults. Notably, all decisions in this study were *independent* of each other, i.e. participants could not learn to improve their decisions with time.

We extended the findings of Pachur et al. (2017) in several ways: first, we showed that age-related changes exist not only during the process of evaluating single decisions, but also in how younger and older humans *learn* from outcomes. Our findings therefore link the age-effects on behavioral decision-making to the rich literature on reinforcement learning. Using RL, we could systematically investigate mechanisms linking outcome history with future decisions (see below). Second, our study investigated decisions from experiences rather than from descriptions, a difference that is known to possibly alter the effects that aging has on choices (Zamarian, Sinz, Bonatti, Gamboz, & Delazer, 2008). Finally, we show that in the context of reinforcement learning OA do not exhibit heightened sensitivity to rare events per se, but rather to events that elicited particularly large prediction errors (i.e., surprise).

Recently, another body of work modeled the influence of extreme/surprising events on decisions using sequential sampling tasks (Spitzer, Waschke, & Summerfield, 2017; von Clarenau, Pachur, & Spitzer, 2022) which are more closely connected to the kind of instantaneous trial-by-trial updating we investigated in this study. These tasks present participants with repeated samples in quick succession from one or more distributions, including extreme samples from the distributions edges, and ask for a judgment of the mean over samples. The results support the idea of selective weighting of extreme outcomes also in the context of a task that is based on a sequential learning process. We believe that also this work is extended by our findings. In particular, we show that similar behavioral patterns emerge also in much slower, single-trial sampling rates and trial-wise choices.

Previous work has also shown that the probability of events that come to mind easily tends to be overestimated (*availability bias*, Tversky & Kahneman, 1973), and that memory for values at the edges of distributions is better (Madan & Spetch, 2012; Madan et al., 2014; Ludvig et al., 2018). This might explain why the distorted probability weighting functions described above. Note, however, that although in our task the low, mid and high outcome distributions differed in their standard deviation, bandits in our task exhibited

similar amounts of low-probability outcomes (see Fig. 1B). Hence the choice between bandits was not conflated by choices between a safe and risky gambles as characterized by different probability profiles. Our work does speak directly to the above mentioned memory biases, and suggest the here reported age-differences could be mediated by memory for extreme outcomes.

Our study is also related to work that has focused on how learning rates are adapted in non-stationary environments, in which the true value of bandits changes over time (Behrens et al., 2007; Nassar et al., 2012, 2010). Unlike our own experiment in which participants learn from bandits with a stable outcome distribution, most of these studies investigated how participants infer the environment's uncertainty and volatility (rate of change), and adapt their learning rates in response to these variables. Our *Surprise* model differs substantially from these accounts in that it assumes no computation of volatility or uncertainty for future use. Rather, the model captures the possibility of instantaneous increase in learning rate when outcomes elicit large prediction errors, with no effects on subsequent learning rates, as would be predicted by uncertainty or volatility-based accounts. Thus, our models are most informative for understanding if surprising events get treated differently in reward-based learning in stationary environments. Most relevant for our study is research that investigated the effects of age on the role of uncertainty and surprise in learning (Nassar et al., 2016). Here, uncertainty was operationalized as a recency-weighted average of absolute prediction errors. According to previous normative accounts, uncertainty should be the dominant driver of learning rates in stationary environments. Surprise, in contrast, captures the immediate effect of an unexpected outcome, i.e. the unsigned prediction error. Although the above mentioned previous work (Nassar et al., 2016) has largely pointed out that older adults tend to underestimate uncertainty, it also found that in response to surprise older adults adjusted their learning rate more than younger adults. Our finding is consistent with the notion that older adults show a heightened sensitivity to surprise, even in the context of stationary outcome distributions. Since our task featured particularly large negative prediction errors, our finding may also offer an explanation for age differences in risk aversion (Albert & Duffy, 2012) that emphasizes transient learning rate driven effects that temporarily affect decision policies.

Computational modelling of participants' behavior was in line with the idea that surprising events are treated differently during learning. A model that allowed for altered (i.e., increased or decreased) updating from surprising events offered the best prediction of participants' choices in low-mid bandit comparisons. One potential limitation of this work was the fact that model parameters did not reflect age differences evident in behavioral analyses. Specifically, the model did not suggest a heightened sensitivity to surprising outcomes that is more pronounced in older adults. A potential reason for this finding might be that the effects of surprising outcomes on participants choices are highly localized. One *inherent* problem in investigating the influence of surprising events in the context of stationary environments is that their number has to be relatively small. This holds the potential danger of model fits that are largely dominated by behavior in which the differential effects of surprise cannot be reflected in participants' choices. To counteract this, we made the likelihood of each model only dependent on the key comparison regarding surprising outcomes. One additional way to address this issue could be to increase the number of bandits in the task that allow for large prediction errors. This might, however, lead to increased task difficulty. Due to the online setting of the task we decided for a more simple paradigm but results have shown that older as well as younger adults perform adequately on the task. Increasing task difficulty in favor of a more fine-grained characterization of the effect of surprising events on choices therefore seems feasible.

There are also additional considerations that concern the fact that our data was collected online via Prolific. The Prolific platform was specifically build to conduct research and requires comprehensive profiles of the participants (Palan & Schitter, 2018), and thus represents an adequate choice to collect data also for older adults. Yet, less control of the experimental environment can lead to increased noise, reflected for instance in lower learning performance (Crump, McDonnell, & Gureckis, 2013). In addition, concerns may be raised regarding how representative older age group on Prolific is. Skilled internet use of OA is more common in populations with higher income and education (Hargittai, Piper, & Morris, 2019) as well as better levels of health and activity (Cresci, Yarandi, & Morrell, 2010). It is therefore likely that the online data collection sampled a slightly different, high-performance population of OA when compared to the population sampled in an offline setting. In line

with this, our data did not show evidence for age differences in general performance, although OA tend to perform worse on reward-based learning tasks (Eppinger et al., 2013; Mell et al., 2005). Since it is possible that an offline setting might lead to more pronounced age differences in our analyses, it would be beneficial to repeat the same experiment in an in-lab setting.

Taken together, this study provides insight into the differential weighting of surprising events during an reinforcement learning task and the role of aging. We found behavioral patterns suggesting that overweighting of extreme events was stronger in the group of older adults which is consistent with findings from risky decision making in the gain domain (Pachur et al., 2017). A model that instantaneously adjusted learning rates based on the surprise of the experienced outcome explained key choices (low-mid bandit trials) better than other candidate models, including an uncertainty model. The model helped to establish an understanding of the learning from surprising events in the context of stationary outcome-based learning. However, the model parameters fell short of explaining the behavioral age differences. Future research should aim to more clearly identify if surprise-related alterations of learning present a general mechanism in the context of stationary environments, or a principle that only gets applied locally to outstanding outcomes and see if the model at hand can be improved to accurately mimic the found behavioral choice patterns.

Data and Code availability

All code related to this work will be published and made openly available at `https://github.com/koch-means-cook/pedlr`. This also includes the code of the task. The data supporting the findings of this study will be made openly available at `https://gin.g-node.org/koch_means_cook/pedlr-main-data.git`.

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Conflict of interest

The authors declare no conflicts of interest.

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F Eigenständigkeitserklärung

Hiermit erkläre ich, dass ich die vorliegende Dissertation selbstständig verfasst und ohne unerlaubte Hilfe angefertigt habe.

Alle Hilfsmittel, die verwendet wurden, habe ich angegeben. Die Dissertation ist in keinem früheren Promotionsverfahren angenommen oder abgelehnt worden.

Christoph Koch

Berlin, 05.12.2022