

PREFRONTAL BRAIN MICROSTRUCTURAL INTEGRITY IS RELATED TO AN EXPLOITATION
BIAS IN OLDER ADULTHOOD

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Abstract

The exploration–exploitation trade-off reflects a fundamental decision-making process supported by interactions between cortical regions involved in reward valuation and monitoring and subcortical systems that regulate attention and learning. In previous work, we demonstrated that microstructural integrity of the locus coeruleus (LC), assessed with quantitative MRI (qMRI), predicts individual differences in explore-exploit behavior in older adults. Building on these findings, we examined whether similar structure–function relationships exist within cortical regions implicated in explore-exploit. In typically aging older adults (N=109), we collected magnetization transfer saturation (MTsat), a qMRI measure sensitive to cellular microstructure, to assess integrity of the medial orbitofrontal cortex (mOFC), frontopolar cortex (FPC), rostral middle frontal gyrus (rMFG), and dorsal anterior cingulate cortex (dACC). Lower MTsat in the mOFC, FPC, and rMFG and decreasing MTsat across time was associated with an exploitation bias. Dominance analysis revealed FPC MTsat as the strongest predictor of exploitative decision-making in older adulthood.

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Background

A key component of daily decision-making involves choosing between exploiting a familiar resource and exploring for new options. To thrive in a dynamic environment, one must adaptively shift between the two depending on context. Do I choose the same brand of food at the grocery store or try something new? Do I stay in the same job or change to something more lucrative, but uncertain? Do I keep skimming an article, hoping for something insightful, or move on to an alternative? The exploration-exploitation trade-off is not only faced by humans in their everyday lives, but by single-celled organisms (Xie & Wu, 2014), birds (Nonacs, 2010), and non-human primates (Costa et al., 2019; Hogeveen et al., 2022). It is a foundational part of animal foraging and the study of ecology (Eliassen et al., 2007; Berger-Tal & Avgar, 2012) and has recently been crucial in developing machine learning algorithms (Gu et al., 2022; Swiechowski et al., 2023). In humans, exploration-exploitation has been studied in both healthy populations (Laureiro-Martinez et al., 2014; Sang et al., 2020; Mata et al., 2013) and clinical populations including those with Alzheimer's disease (AD) (Troger et al., 2019), Parkinson's disease (Djamshidian et al., 2011), autism spectrum disorder and attention deficit hyperactivity disorder (Gilga et al., 2018), schizophrenia (Cathomas et al., 2021), and substance use disorders (Addicott et al., 2014; Morris et al., 2016; for a review of psychiatric research see Addicott et al., 2017 & see Wyatt et al., 2024).

In laboratory settings, researchers have studied this trade-off across the task domains of reinforcement learning, information search, and foraging. While this thesis focuses on foraging as the primary assay of explore-exploit decision-making, I will begin with an overview of each of these explore-exploit domains, including the types of laboratory tasks

used, how they are analyzed, and the brain regions that have been implicated in explore-exploit decision-making within those domains. Following this review, I will discuss the Shifting Mental Mode (SMM) hypothesis of aging cognition (Turner et al., 2021). The SMM hypothesizes that a bias towards exploitation emerges in older adulthood due to age-related neurocognitive changes, a foundational premise of this thesis. I will conclude this overview with a summary of recent work from our laboratory examining the microstructural integrity of the Locus Coeruleus (LC) in healthy older adults and its relationship to an age-related exploitation bias. This work sets the stage for the current study which investigates the hypothesis that an age-related exploitation bias is associated with microstructural integrity of cortical brain regions implicated in explore-exploit decision-making.

Domains of explore-exploit decision-making

Reinforcement learning

Reinforcement learning (RL) tasks are the most common tasks used to study the explore–exploit trade-off, with broad applications across disciplines including psychology, computational neuroscience, machine learning, and branches of applied mathematics such as control theory (Sutton & Barto, 2015). Within psychology and computational neuroscience, reinforcement learning is considered a type of reward-based learning where the goal of an agent is to maximize their reward by sampling different options. These options usually take the form of slot machines or ‘bandits’ creating a scenario akin to gambling at a casino. The number of bandits usually ranges from two to four and the agent can freely sample each machine over a given number of trials to identify which machine provides the

highest rewards. The reward distribution for each bandit is stochastic, typically generated by drawing from a Gaussian distribution where the mean is either fixed (stationary bandit) or changes across time (non-stationary bandit) by adding diffusion noise (Daw et al., 2016; Laureiro-Martinez et al., 2014).

To identify which bandit is the most rewarding at any given time an agent must sample each option. As an agent samples a machine, they learn its value, aiming to discover and exploit the most rewarding option at that point in the task. Performing well requires tracking both the immediate expected value (IEV) and future expected value (FEV) of all available options (Hogeveen et al., 2022). The IEV reflects how rewarding an option is based on past experience, while the FEV captures uncertainty and how much could still be learned about the option. Options that are frequently sampled tend to have lower FEVs, as their IEVs are better known, whereas infrequently or recently unsampled options carry higher FEVs. Selecting the current option (with higher IEV) is categorized as exploitation, decisions to explore based on the highest FEV are typically referred to as ‘directed exploration’, all other explore decisions are referred to as ‘random exploration.’

In directed exploration, the aim is to reduce uncertainty, thus exploration is *directed* towards the option that will provide the most information (Wilson et al., 2021). This will be the option that has not been recently sampled with the highest FEV. Conversely, random exploration involves sampling options unpredictably, or by adding decision noise, which randomly increases the value of options, regardless of their IEV. Effectively modelling these different types of exploration alongside exploitation requires estimating latent variables

such as IEV and FEV, which are not directly observable. To do this, researchers have developed computational modelling approaches that generate testable hypotheses about the mechanisms underlying explore-exploit and support inferences about the neural computations involved.

A variety of computational algorithms have been developed to mimic how agents solve reinforcement learning problems (Wilson et al., 2021). The most commonly used include: 1) the epsilon-greedy algorithm, which exploits the option with the highest IEV while adding minimal random exploration; 2) the upper confidence bound (UCB) algorithm, which engages in directed exploration by favoring options that have been sampled less frequently (high FEV), where the information bonus is based on the posterior distribution and typically set to twice the standard deviation; 3) softmax exploration, which exploits the option with the highest IEV but adds random decision noise to the value of each option, allowing for occasional exploration; and 4) Thompson sampling, which is similar to softmax exploration, but the decision noise scales with each option's uncertainty, so as uncertainty decreases, exploration also decreases. While humans likely make use of each of these 'strategies' depending on both the environment and individual differences, how much humans value reward versus reducing uncertainty has been greatly debated in the reinforcement learning literature (Daw et al., 2006; Wilson et al., 2014; Blanchard & Gershman, 2018; Gershman, 2018; Schulz & Gershman, 2019; Horvath et al., 2021; Hogeveen et al., 2022).

The seminal study by Daw et al. (2006) found that humans use softmax exploration in a four-armed bandit task with non-stationary bandits and linked these model-derived

parameter estimates to cortical function. However, this finding has been criticized because the task does not reliably dissociate reward from information (Wilson et al., 2014). When an option is sampled, the participant receives a reward and simultaneously learns about the underlying distribution. In this design, reward and information co-occur simultaneously. As a result, the use of strategies such as UCB and Thompson sampling, which rely on gaining information and reducing uncertainty, may be masked when reward and information are confounded.

To address this issue, Wilson et al. (2014) developed a two-armed bandit known as the horizon task. The task provides differential information about each bandit before the participant makes a choice and manipulates the number of choices (the time horizon) a participant is given on each trial. By controlling how much information participants receive and varying the horizon length (either short: 1 trial, or long: up to 6 trials) researchers can assess how exploration strategies shift based on context. On longer horizons, participants prioritized FEV, engaging in directed exploration (UCB) by sampling the option they had less information about. On shorter horizons, they focused on IEV, choosing the option they believed to be most rewarding. These findings showed that humans use directed exploration and can prioritize information over reward depending on the decision context. This includes the agent's temporal horizon, which is further discussed in regards to hypothesized age-related exploitation biases below.

Several studies have expanded this finding, showing that humans attend more to reward than information in highly rewarding contexts (Dezza et al., 2017, 2022), and that they

use both UCB and Thompson sampling flexibly based on uncertainty (Gershman, 2018). Crucially, when reward and information are fully decoupled in a neutral environment, uncertainty appears to be the primary driver of explore-exploit behavior (Horvath et al., 2021). Taken together, these findings suggest that the field of reinforcement learning may increasingly focus on linking specific strategies to the environments they are best suited for, rather than searching for a single global strategy to explain all behavior. Additionally, across strategies, both the FEV and IEV of options appear to play a consistent role. Recent work shows that both humans and macaque monkeys attend to FEV and IEV, and that these parameters are differentially encoded in the human and macaque brain (Hogeveen et al., 2022).

At the neural level, exploitative decisions based on IEV are associated with activation in the ventromedial prefrontal cortex (vmPFC), which is thought to reflect the degree of certainty about the value of a choice option (Boorman et al., 2019; Kolling et al., 2012). For example, when prediction errors are low and the environment is stable, exploitation is ideal, and the vmPFC appears to support this process. In contrast, exploratory decisions have been associated with activation in the frontal polar cortex (FPC), anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC), and several other cortical regions involved in frontoparietal control and attention networks (Laureiro-Martinez et al., 2014; Tomov et al., 2020; Wyatt et al., 2024).

The FPC has been shown to encode FEV by tracking the information value of other choices, with activity decreasing once a high FEV option is selected (Hogeveen et al., 2022).

This supports theories of FPC function that suggest the FPC monitors multiple goals and helps switch between goal states (Mansouri et al., 2017). Similarly, the ACC tracks the value of different choice options and facilitates the shift to exploration when another option exceeds the current one in value (Blanchard and Gershman, 2018), potentially by overriding the current behavior (Shenhav et al., 2013). While the ACC may track both IEV and FEV, the FPC seems to track FEV specifically (Hogeveen et al., 2022), though more research is needed to fully elaborate this association. Finally, the dlPFC has been linked to FEV and model-based control. Hogeveen et al. (2022) suggest that when uncertainty is high and options have high FEVs, the dlPFC supports model-based decision-making by constructing an internal model of the task environment. This is consistent with prior work showing that the dlPFC plays a central role in executive functions, such as working memory and tracking task demands (Lemire-Rodger et al., 2019).

Information search

Information search shares many similarities with reinforcement learning, as both involve sampling several options to identify the most rewarding option. A key distinction is that in information search, once a threshold is reached, the agent stops exploring and switches to exploitation, ending the search for new information (Chin et al., 2015). A contemporary, real-world example of this form of exploration-exploitation decision-making would be internet searching. A person might sample multiple websites or scroll through the results of a Google query until they identify a site containing the information they need. After this point, they may stop exploring and exploit the site they have found. Continued

exploration requires more time, and when determining their criterion to stop exploring, humans typically use a linearly decreasing value threshold (Sang et al., 2020). This means that as time passes, humans become more willing to settle for a proportionally less valuable source of information or reward. Information search could be considered a sub-domain of reinforcement learning as many of the principles are the same, however, information search tasks are much less frequently reported as an experimental paradigm to assay explore-exploit decision-making.

The most widely used task paradigm to examine information search is the Secretary Task, in which participants sequentially evaluate a set of candidates for a fictional job (Ferguson, 1989). Participants can continue to view candidates (explore) or hire the current candidate (exploit), forgoing any further exploration. While these tasks are useful for examining optimal stopping problems, their ecological validity has been questioned. In real-world information search, agents often retain the flexibility to continue exploring even after exploiting a resource. For example, in a hiring context, a decision-maker may be favouring one candidate, indicating exploitation, but may still wish to view additional applications or revisit ones they previously rejected. To address this, recent information search tasks allow flexible switching between exploration and exploitation, while still maintaining an optimal stopping criterion (Sang et al., 2020).

Another class of information search tasks, known as observe-or-bet tasks, incorporates elements of both information search and reinforcement learning by having participants switch between sampling options for information and sampling for reward

(Tversky & Edwards, 1966). These tasks can be designed to feature either static environments, which encourage front-loaded exploration followed by exploitation, or dynamic environments, which require ongoing shifts between exploration and exploitation. Humans tend to use noisy exploration strategies (akin to random exploration) that are well suited to dynamic real-world environments (Navarro et al., 2016), but they are also capable of adapting to front-loaded exploration strategies if given enough time, once again showing that humans can adaptively adjust their strategy to the environment.

There is very little research examining the neural basis of information search and the few published reports show overlap with reinforcement learning and foraging (see below). Observe or bet paradigms have been associated with activation of the ACC, related to tracking the value of alternative choices (Blanchard & Gershman, 2018). Additionally, the cost of switching from exploitation to exploration has been associated with both ACC and ventral striatum (Kolling et al., 2019). More research is needed to both understand the brain regions that underlie information search and disentangle the mechanisms of information search from reinforcement learning and foraging.

Foraging

Foraging has been present throughout our evolutionary history and is a fundamental decision animals face in the wild when searching for food, mates, and shelter (Hills et al., 2006). In its standard form, foraging involves deciding how long to exploit a useful but declining resource before seeking a new one. In nature, resources are typically organized in ‘patches,’ areas containing a high density of rewarding objects (Todd & Hills, 2020). As a

patch becomes depleted, an animal must weigh the value of continuing to exploit the current patch against exploring new patches. This choice carries risk because switching patches incurs a travel time during which no resources are obtained. Additionally, the availability of resources in other patches remains unknown until sampled. Optimal foraging requires weighing the current rate of return against the potential costs of leaving and the uncertain value of alternative patches.

Optimal patch-leaving decisions are described by the Marginal Value Theorem (MVT; Charnov, 1976), which predicts that an animal should leave its current patch once the reward rate within that patch drops below the average reward rate of the broader environment. Thus, foraging optimally requires tracking two crucial pieces of information known as the current reward rate (CRR) and average reward rate (ARR). Humans have also been shown to follow MVT when facing analogous foraging problems both in the external environment (Wolfe, 2013; van Dooren et al., 2021) as well as during mental searches (e.g. finding an item in memory; Hills et al., 2013; Lundin et al., 2023). In daily life, humans often face foraging-like decisions where the resources being optimized are not food, but time, money, or information.

Typical laboratory foraging tasks involve foraging for berries, fish in a pond, treasure, or other resources (Louapre et al., 2010; Mata et al., 2009; Wiegand et al., 2019; Wolfe, 2013; van Dooren et al., 2021). Deviations from optimal foraging behavior have been observed in opioid addiction (Raio et al., 2022) and healthy aging (Mata et al., 2009; Mata et al., 2013; Wiegand et al., 2019). Interestingly, about 25% of individuals in a healthy sample

demonstrated superior foraging abilities (Johannesson et al., 2017). Together, these findings suggest that foraging tasks are sensitive to both group and individual differences, and performance may reflect broader abilities to navigate real-world explore-exploit decisions.

There are very few studies examining the neural basis of foraging. Similar to reinforcement learning and information search, foraging decisions are associated with ACC activation (Kolling et al., 2012; Hayden et al., 2011). The ACC has also been implicated in the broader risk-based decision-making literature (Krain et al., 2006) and appears to encode both the average value of the environment, and the costs associated with switching away from the current patch. The ventromedial prefrontal cortex (vmPFC) has also been implicated, though to a lesser extent, in representing the values of well-defined patches (Kolling et al., 2012). When foraging-in-mind (e.g., semantic memory retrieval), the hippocampus and posterior cerebellum have been shown to play a role during patch switches, with activity in these regions increasing monotonically before a switch takes place (Lundin et al., 2023).

While each of these categories of explore-exploit tasks measures the broad trade-off of ‘should I stay or should I go’, the underlying computations of each task differ, which may explain why behavioural performance across explore-exploit task domains did not load onto a single general factor in a recent report (von Helversen et al., 2018). However, patterns of brain activity considerably overlap across these three explore-exploit domains (Wyatt et al., 2024). Moreover, the same region can encode features of both exploration and exploitation (Hogeveen et al., 2022), suggesting that shared brain regions across domains may support different neurocomputations depending on the task context. As noted earlier, foraging is the

primary measure of explore-exploit decision-making used here to test the exploitation bias hypothesis in older adulthood and associated neural mechanisms. As a future direction, this line of research will investigate whether an age-related exploitation bias exists across these other explore-exploit task domains (see concluding section below).

Explore-Exploit decision-making in older adulthood

One area that remains relatively understudied is how the exploration–exploitation trade-off changes across the adult lifespan and into older adulthood. The SMM hypothesis of aging (Spreng & Turner 2019, 2021) is a neurocognitive model proposing that adults become increasingly biased toward exploitation-based decision-making over the adult life-course. According to this model, the shift is driven by the interaction of several age-related changes, including the accumulation of prior knowledge, declines in cognitive control, a narrowing of time horizons, a greater emphasis on affective goals, as well as alterations in subcortical neuromodulatory regions related to attention and reward processing and cortical networks implicated in internally-directed as well as goal-directed cognition. Together, these age-related changes produce a bias toward exploitation that can be either adaptive or maladaptive, depending on the decision-making context. A key feature of the SMM is that it integrates both age-related cognitive losses, such as declining executive functioning, and age-related cognitive gains, such as expanded prior knowledge and lived experience, which are often overlooked in typical neurocognitive aging studies. Moreover, this model incorporates known age-related changes in socioemotional functioning as well as motivational drive.

Increased prior knowledge

One proposed driver of increased exploitation in older adulthood is the accumulation of prior knowledge. It is a well-replicated finding that semantic knowledge increases with age (Park et al., 2001; Verhaeghen, 2003; Grady, 2012), and this may contribute to older adults placing less value on exploration compared to younger adults. As one's understanding of the world grows, the relative returns on exploration diminish, since new information is more likely to be redundant or irrelevant to an affectively biased goal hierarchy (Mather & Carstensen, 2005), while the time horizon to amortize gains or losses narrows.

One of the primary functions of exploration is to acquire information, and much of childhood and adolescence may be viewed as a period of front-loaded exploration aimed at building the foundational knowledge needed for adulthood (Schulz et al., 2019). During this developmental period, individuals readily forgo immediate rewards in favor of gaining information about the world around them which holds long-term value. In adolescence and early adulthood, there is a shift away from random exploration toward more strategic, directed exploration (Somerville et al., 2017). However, this trend does not continue indefinitely. Older adults exhibit declines in both random exploration (Mizell et al., 2024) and directed exploration (Meder et al., 2021; Wu et al., 2018), a shift that may be driven in part by the increasing utility of leveraging accumulated knowledge.

In this sense, exploration across the lifespan may mirror an optimal stopping process. When sufficient information has been accumulated, further exploration yields diminishing returns, and the costs (or risks)—such as time, effort, or uncertainty—begin to

outweigh the benefits of known rewards. For older adults, the decision to exploit may reflect not only changes in cognitive function but also a rational response to having already built a robust internal model of the world.

Decreased cognitive control

In addition to accumulated knowledge, age-related declines in cognitive control are thought to play a key role in the shift toward exploitation in older adulthood (Spreng & Turner, 2019, 2021, for reviews). Cognitive control refers broadly to the capacity to direct thought and behavior in alignment with goals and includes executive functions such as working memory, inhibition, and cognitive flexibility. As these abilities decline with age, older adults may find it more difficult to manage the demands of exploratory behavior, which is often more cognitively taxing than exploitation (Chin et al., 2015; Baror & Bar, 2016).

One strategy for balancing exploration and exploitation is selective maintenance, where the values of options are actively maintained in working memory. This process becomes less efficient with age, potentially impairing the ability to track fluctuating value signals and to switch flexibly between options (Hallquist & Dombrovski, 2019). Evidence from foraging tasks supports this idea: older adults tend to remain in depleted patches longer than is optimal, suggesting a reduction in cognitive flexibility (Mata et al., 2009; Wiegand et al., 2019). These patterns are consistent with the broader claim that exploratory decision-making places greater demands on executive control, and that age-related declines in these functions contribute to a generalized bias toward exploitation.

Although direct evidence linking cognitive control deficits to exploitative choice strategies remains limited (Mata et al., 2013), a growing number of studies show that when cognitive demands increase, both younger and older adults tend to adopt more exploitative approaches (Chin et al., 2015; Baror & Bar, 2016). This suggests that exploitation may be a default strategy that emerges when cognitive resources are constrained, either acutely or chronically with age. In this view, the decline in cognitive control across the lifespan not only reduces the capacity to explore but also increases the likelihood that individuals will rely on less demanding, more familiar exploitative strategies.

Shifting time horizons and affectively-biased goal hierarchies

As noted earlier, the human developmental trajectory can be viewed as one of front-loaded exploration followed by exploitation. This transition may be adaptive, in part, because as individuals age, they have less time to reap the benefits of new information, and the risks associated with exploration begin to outweigh the potential gains (Sherratt & Morrand-Ferron, 2018; Carstensen, 2006). This may help explain why older adults are generally more averse to novelty (Sakaki et al., 2018), particularly when uncertainty about potential rewards is high (Nussenbaum et al., 2023).

Socioemotional Selectivity Theory (SST) encapsulates this idea by proposing that as time horizons narrow, older adults increasingly prioritize emotionally meaningful goals. This leads to a preference for outcomes that are positively valenced and rewarding, rather than those aimed at information acquisition or long-term learning (Carstensen, 2006; Charles and Carstensen, 2010). Supporting this shift, older adults tend to show greater sensitivity to

gains and reduced sensitivity to losses, patterns linked to changes in underlying neural circuitry involved in reward processing (Samanez-Larkin and Knutson, 2015).

In sum, the SMM hypothesis posits that increasing stores of prior knowledge, declines in cognitive control, reduced time horizons, and an emphasis on affectively rewarding goals jointly contribute to an exploitative mental mode in older adulthood. These factors interact to reinforce a bias towards exploiting known rewarding options over exploring uncertain alternatives. At the same time, this process is influenced by age-related changes in brain structure and function.

Explore-exploit decisions in pathological aging

Studying age-differences in explore-exploit decision-making raises the question as to whether any observed biases or sub-optimal choice behaviours reflect typical age-related changes or may signal incipient age-related brain disease. There is evidence for exploitation biases in AD and mild cognitive impairment (Auriacombe et al., 2006; Pakhomov et al., 2016; Troger et al., 2019), as well as frontotemporal dementia (Strenziok et al., 2011). In Parkinson's disease elevated dopamine levels have been linked to an exploratory decision-making bias (O'Sullivan et al., 2011; Voon et al., 2010), suggesting that depletion may have the opposite effect and promote a bias towards exploitation. Separate studies examining the impact of low dopamine levels also support this idea (Addicott et al., 2014; Harle et al., 2015; Thiruchselvam et al., 2017). Taken together, this evidence raises the possibility that exploitation biases in later life could be associated with typical aging or signal a more pathological aging trajectory, a question explored later in the thesis.

Neural correlates of age-related foraging biases: Locus coeruleus microstructural integrity

The LC is an ensemble of neurons located in the pontine tegmentum of the brainstem. It is the primary site for the synthesis of norepinephrine (NE) in the brain and serves as a regulator for noradrenergic signalling. NE projections from the LC regulate the brain's attentional system, optimizing attention for current environmental demands via tonic and phasic LC firing patterns (Aston-Jones & Cohen, 2005). In the context of explore-exploit choices, tonic LC activity is associated with exploration for alternative behavioral strategies or sources of reward and disengagement from the current task. In contrast, phasic LC activity is associated with exploitation and behavioral optimization during ongoing task performance. The switch between tonic and phasic LC firing is mediated by projections from frontal regions such as the orbitofrontal cortex and anterior cingulate cortex, which signal information about task performance and utility. Thus, when task utility is high, phasic LC firing promotes exploitation, task optimization, and action learning. This occurs in part through connections with dopamine mediated reinforcement learning systems that strengthen behaviors leading to reward. Alternatively, when task utility is low or the source of reward is depleted, the LC shifts towards tonic firing and promotes exploration, visual search, and the execution of novel behaviors.

The SMM hypothesis of aging posits that in older adulthood, changes in LC integrity and function reduce the flexibility of the LC-NE system resulting in sluggish switching between phasic and tonic firing modes. These changes may be attributable to age-related structural changes, including accumulation of tauopathies, a pathological hallmark of AD

(Braak & Braak, 1991), and changes in projection systems from the LC to the cortex. In the context of the neurocognitive and socioemotional changes that bias older adults towards exploitation, the SMM predicts that changes in LC would reduce older adults' capacity to switch from phasic to tonic firing modes, thereby exacerbating prepotent age-related exploitation-biases.

To test this prediction, in a recent study we used a multiparametric mapping MRI sequence which includes a measure of magnetization transfer saturation (MTsat; see below) to examine how the microstructural integrity of LC was associated with performance on a foraging measure of explore-exploit decision-making in older adults (Turner et al., 2024). Consistent with predictions, we observed an age-related exploitation bias in older adulthood. Further, the microstructural integrity of LC was lower with older age and, critically, this measure was robustly associated with an exploitation bias during foraging (Turner et al., 2024).

Measuring subcortical and cortical microstructure

As the primary neural measure in the thesis is microstructural integrity, this section describes how this is measured using advanced MR imaging techniques. Quantitative MRI (qMRI) is an alternative to standard, contrast-based MRI measures that allows researchers to examine neural structures and processes *in vivo* using quantitative markers. Unlike contrast-weighted MRI, where images are interpreted visually and signal intensity values are arbitrary, qMRI produces numerical values that reflect specific properties of neural tissue (Radunsky et al., 2024). These values enable the creation of parametric maps with higher

sensitivity to detect subtle differences that may not be captured by contrast-based approaches. Further, qMRI measures show high reliability both within individuals across multiple sessions and across different imaging sites (Weiskopf et al., 2013; Leutritz et al., 2020). MTsat is a qMRI measure thought to index tissue microstructure and is the core assay of tissue microstructure reported in the thesis.

MTsat builds on magnetization transfer (MT) imaging, which is an MRI technique based on the exchange of magnetization between the protons in free water and protons bound to macromolecules, such as neuronal proteins and lipids found in the phospholipid bi-layer of cells and myelin. Because macromolecular protons have very short T_2 relaxation times, they produce very little signal and are difficult to image. However, by using an off-resonance radiofrequency pulse (MT pulse), it is possible to selectively saturate these bound protons without affecting free water protons. Some of this saturation is transferred to nearby free water protons, causing them to become saturated and reducing their signal. When a standard excitation pulse is then applied at the resonance frequency of free water, the resulting signal is reduced based on the pre-saturation from the magnetization effect. Comparing signal intensity before and after the MT pulse provides a contrast that reflects tissue microstructure, particularly macromolecular content.

Although commonly used in medical imaging, specifically for myelin imaging in multiple sclerosis (Schmierer et al., 2004, 2007), MT ratio and similar metrics have also been used to relate brain structure to behavior (Allen et al., 2017, Steiger et al., 2016, Dahl et al., 2022), and are typically considered to index myelin density (Underhill et al., 2011; Khodanovich et al., 2017; Ziminski et al., 2013; Carradus et al., 2020). While useful, standard

MT contrast is dependent on sequence parameters and is influenced by T_1 relaxation times and flip angle inhomogeneities (Helms et al., 2008). To overcome this limitation, magnetization transfer saturation (MTsat) was developed as part of the multiparameter mapping (MPM) qMRI protocol. MTsat is a semi-quantitative measure of the MT effect that incorporates additional reference scans such as proton-density and T_1 -weighted images to reduce the impact of T_1 relaxation and radio-frequency field inhomogeneities. Although MTsat does not directly measure an absolute biological property such as myelin content, it is similar to qMRI-derived MPM metrics in that it is highly reliable across sites and timepoints, demonstrating the highest reliability of qMRI metrics (Wenger et al., 2022). In addition, MTsat has been shown to be sensitive to age-related changes in tissue microstructure and brain atrophy (Draganski et al., 2011), making it a novel structural assay that can be used to examine the aging brain.

Neural correlates of age-related foraging biases: Cortical microstructural integrity

Building upon our findings relating foraging to LC microstructural integrity (see above), the current study sought to examine how tissue microstructure (indexed by MR-derived MTsat) in cortical brain regions previously implicated in explore-exploit decision-making is associated with foraging performance in older adulthood. As mentioned previously, there is very little neuroimaging work examining the brain regions that underpin foraging, and no prior research has examined the relationship between cortical microstructure and foraging. In a recent meta-analytic review of fMRI studies, we identified a set of cortical brain regions that were consistently activated during exploration and exploitation-based choice (Wyatt et al., 2024; Figure 1). For the present study, we selected a

subset of the regions identified in this review, which have been the most commonly reported in neuroscience investigations of explore-exploit decision-making. Two regions, ventromedial prefrontal cortex (vmPFC) and orbitofrontal cortex (OFC), are associated with exploitation-based choice; two additional regions, frontopolar cortex (FPC) and rostral middle frontal gyrus (rMFG), are associated with exploration-based choice. Additionally, we included the dorsal anterior cingulate cortex (dACC), as it has been strongly implicated in models of explore-exploit decision-making (Aston-Jones & Cohen, 2005), specifically in foraging contexts (Kolling et al., 2012).

Meta-analytic Results & Cortical Regions Under Investigation

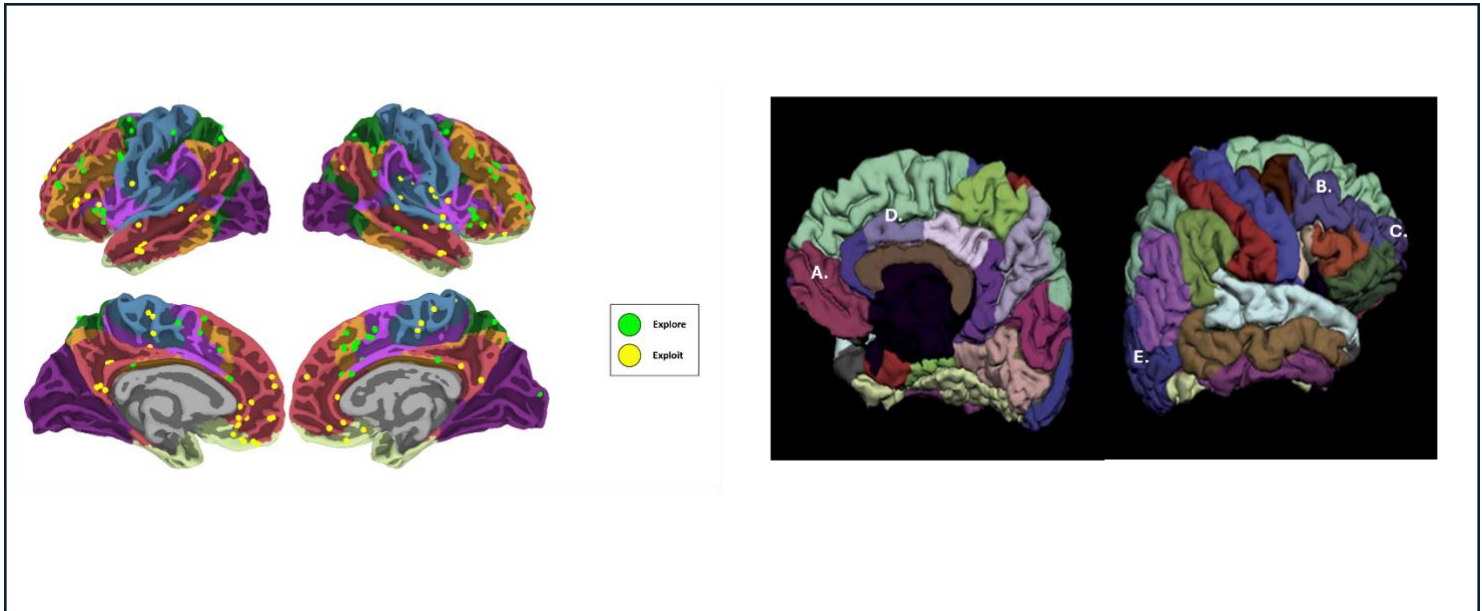


Figure 1: Left panel shows meta-analytic results depicting regions active during exploration-exploitation based choice. Right panel shows the selected cortical regions based on the Desikan-Killiany atlas. Identified ‘core’ regions include A: mOFC; B: rMFG; C: FPC; D: dACC. E: lateral occipital lobe (LO) was included as a control region.

The objective of the thesis was to extend our earlier work examining the relationship between brain microstructure and explore-exploit based choice in older adults by investigating whether MTsat in these cortical regions displays a similar relationship to foraging as previously reported for the LC. Specifically, we examined whether MTsat is a more robust predictor of foraging performance, and an exploitation-bias, as compared to standard measures of cortical macrostructure (e.g., cortical thickness), and which of the cortical regions of interest were mostly reliably associated with foraging behavior. Consistent with our previous findings in LC, we predicted that lower cortical MTsat, and declining MTsat over time, would be reliably and specifically associated with an exploitation bias during foraging in older adulthood. We predicted that these associations would be most robust in frontopolar cortices, the cortical region most reliably implicated in explore-exploit choice; and these associations would be observed over and above associations with cortical macrostructure. Finally, we predicted that APOE4 phenotype and positron emission tomography (PET) markers of AD risk would be associated with a greater exploitation-bias and poorer microstructural integrity, consistent with earlier studies.

Materials and methods

Study participants

137 participants from the PResymptomatic EValuation of Experimental or Novel Treatments for AD (PREVENT-AD) cohort were included in this study. The PREVENT-AD cohort is a longitudinal cohort composed of cognitively healthy older adults who have a parental or multiple-sibling history of AD (see Tremblay-Mercier et al., 2021). Beginning in

2011, participants in this cohort have undergone cognitive and genetic testing, extensive multi-modal neuroimaging, and biofluid sampling. For inclusion in the current study, participants required one time point of qMRI data collected between January 2019 to January 2020, and/or October 2021 to November 2022. Additionally, participants must have completed the berry foraging task (see below), which was introduced during the second data collection wave. All participants gave informed written consent before participating in the study and the procedures of the PREVENT-AD study were approved by the McGill institutional review board and/or the Comité d'éthique de la recherche du CIUSSS de l'ouest de l'île de Montréal.

From this sample, a smaller sample of 118 participants had two qMRI scans and successful completion of the foraging task and were included in subsequent analyses (except the linear-mixed effects regression, see below). Additionally, 2 participants were excluded due to foraging outlier performance using an interquartile range outlier calculation (Hoaglin, 2003). These participants either did not complete the task or were unable to control the avatar effectively. An additional 9 participants were excluded due to poor imaging data or registrations. The final sample consisted of 109 participants, with a mean age of 70 years (range: 60-88 years), comprising 77 females and 32 males (See Table 1 for demographic information). The mean elapsed time between scans was 2.7 years (range: 1.8-3.6 years).

Behavioral task

Participants completed a timed computer-based foraging task that required them to collect berries in a simulated foraging environment (van Dooren et al., 2021). They controlled

a small avatar and were instructed to collect as many berries as possible by moving between an aerial screen in which they uncovered berry patches (Figure 2a), and a zoomed-in view of an entered patch (Figure 2b). Once they uncovered and entered a patch, their avatar was replaced with a hand icon, which they could maneuver to collect berries by moving the hand across the patch. Participants could freely enter and leave patches according to their preference, allowing them to switch from exploiting a current patch to exploring for new patches. Additionally, participants were free to return to previously uncovered patches, simulating a realistic foraging environment. Behavioral data were analyzed using Marginal Value Theorem (MVT; Charnov, 1976) using previously reported methods (Turner et al., 2024; van Dooren et al., 2021) which are briefly summarized here.

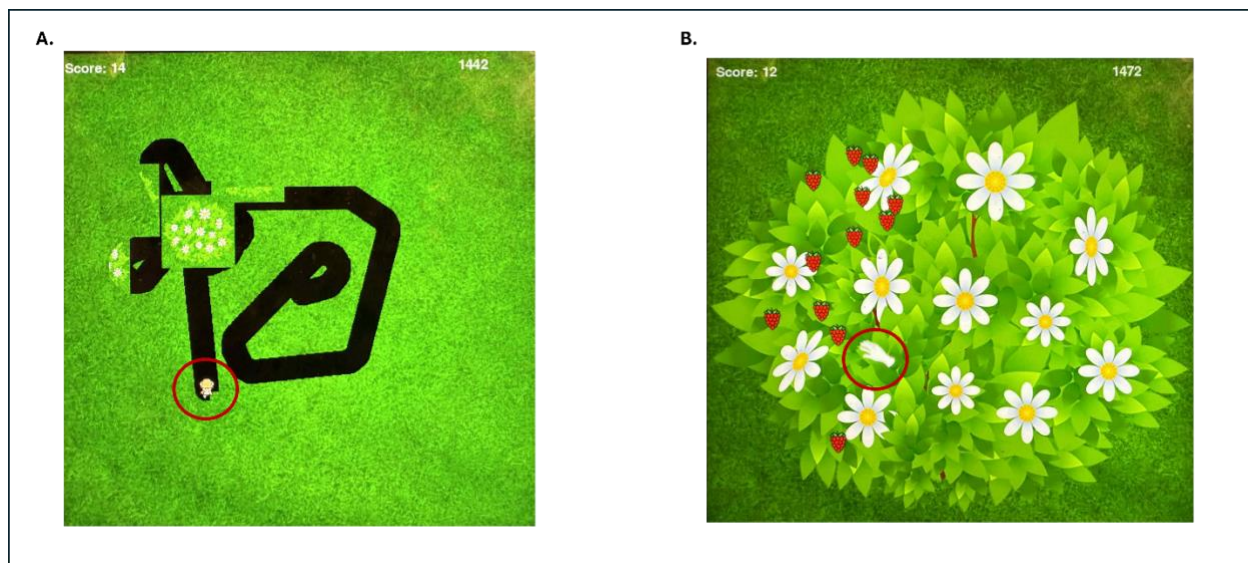
Berry Picking Game

Figure 2: Panels depicting the berry foraging game from van Dooren et al., (2021). For clarity, the participant-controlled avatar and hand are circled in red for this figure. A: Overworld screen. Overworld traversal generates a black trail denoting where the participant has searched. Berry patches are marked with a set of flowers. B: Patch screen.

According to MVT, a participant should leave a patch when their current resource intake rate, referred to as the CRR, equals the average resource intake rate for the environment, known as the ARR. To compute optimal foraging behavior, we first needed to determine the appropriate time window for calculating CRR. We did this by iteratively fitting each participant's foraging run using multiple time windows. For each patch visit, we identified the interval that minimized the difference between the predicted optimal leave time and the participant's actual leave time. This difference was defined as the leave time difference (LTD).

We tested 200-time windows ranging from 0 to 20 seconds in 100-millisecond increments and found that a 19.5-second window minimized LTD at the group level. To confirm this, we conducted a follow-up analysis using 50 windows ranging from 19.25 to 19.75 seconds and again found that 19.5 seconds was the optimal interval. This value was then used to calculate each participant's LTD. Positive LTD values indicate a bias toward exploration, meaning the participant left earlier than optimal. Negative LTD values indicate a bias toward exploitation, meaning the participant stayed in the patch longer than optimal.

Sample Demographics and Foraging Measures

A) Demographics	
N	109
Age (years)	70.1 (4.7)
Education (years)	15.3 (3.0)
Sex	
Female	77
Male	32
APOE genotype	
APOE4 positive	45
APOE4 negative	63 (1 N/A)
B) Foraging Measures	
Leave Time Difference	0.7 (15.3)
SD of Individual Leave Time Differences	24.5

Table 1: A) Demographic information for the sample used. 1 participant did not have APOE4 data. B) Descriptive statistics for the foraging task.

Neuroimaging protocols

All neuroimaging was collected on a 3T Siemens PrismaFit at the Douglas Research Centre. The custom multi-parametric mapping sequence was provided by the McConnell Brain Imaging Centre of The Neuro. Sequence parameters and processing steps have been reported elsewhere (Wearn et al., 2024; Turner et al., 2024) and are replicated here for ease of reference. T1w MPRAGE: 1mm isotropic, TR/TE/TI=2300/2.96/900ms, FA=9°; MTsat: three multi-echo sequences (1mm isotropic, total TA=17:30) with predominant weighting for: T1 (TR=18ms, 6 echoes, TE=2.16-14.81ms, FA=20°), magnetization transfer (MT) (TR=27ms, 6 echoes, TE=2.04-14.89ms, FA=6°, MT pulse FA=540°, 2.2kHz off-resonance, 12.8ms) and proton density (TR=27ms, 8 echoes, TE's=2.04-22.20ms, echo-spacing=2.57ms, FA=6°). B1+ maps were acquired with a double-angle method using segmented EPI with the following parameters: TE/TR = 46/4010ms, 35 slices, FOV = 256 mm, 2x2x4 mm resolution, FA's=60,120°, TA=2:16. Whole brain volumes were calculated from Freesurfer grey and white matter volume estimates of the cerebrum derived from the MPRAGE.

MPM Processing

B1+ maps were created in qMRLab using the double-angle method with a sixth-order polynomial smoothing kernel. All further processing of MTsat maps was performed using the hMRI toolbox (v 0.4.0). Maps for MTsat were corrected for B1 – receive field inhomogeneities, calculated from two PD-weighted turbo-flash sequences acquired using a 32-channel head coil, with otherwise identical acquisition parameters (2 mm isotropic resolution, TR/TE = 344/1.55 ms, FA = 3°, TA = 0:35). Default hMRI toolbox settings were used. Parameter maps were denoised using ANTS DenoiseImage.

Regions of Interest

The Desikan-Killiany atlas was used (Desikan et al., 2006) to identify each cortical ROI and control region. The mOFC subdivision from the atlas encompasses both core exploit ROIs that were identified in our previous study (vmPFC, OFC) so the mOFC designation from the atlas was used for subsequent analyses. MTsat and cortical thickness values for each ROI were combined across hemispheres, as there were no predictions related to lateralization. LC was defined using previously validated atlases thresholded at 10% (Wearn et al., 2024; Ye et al., 2021).

Genotyping

APOE4 genotyping methods for participant genotyping have been described previously (Tremblay-Mercier et al., 2021). Briefly, genomic DNA was extracted from 200 µl of whole blood using the QIASymphony automated platform along with the QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA), following the manufacturer's standard protocol. Genotyping for APOE polymorphisms, specifically rs429358 and rs7412, was carried out using either pyrosequencing (via PyroMark24 or PyroMark96 systems) or Illumina-based DNA microarray analysis. Due to the limited number of individuals with the e4/e4 genotype, participants were categorized as APOE4– (no e4 alleles) or APOE4+ (carrying one or more e4 alleles).

Statistical Analysis

To examine longitudinal changes in brain structure, the annualized percent change (APC) was calculated for each ROI for both MTsat and cortical thickness. To compute

annualized percent change, we used a compound growth formula that assumes proportional (multiplicative) change over time. Specifically, the formula:

$$\left(\frac{x_B}{x_A}\right)^{\frac{365}{t_B - t_A}} - 1$$

calculates the rate of change that would occur over a one-year period, assuming the relative change between timepoints A and B continues at a constant rate. Here, x_A and x_B are the values at timepoints A and B respectively, and $t_B - t_A$ is the number of days between measurements. This method accounts for variable time intervals between assessments and expresses change as a standardized yearly rate. To examine cross-sectional relationships with MTsat, values from time point 2 were selected as these were temporally coincident with collection of the foraging data.

Correlations were used to examine the relationships between MTsat values in each ROI and: 1) demographic variables (age, education, sex); 2) MTsat values in the LC. Following this, partial correlations were conducted between the MTsat APC and time point 2 data with LTDs. Partial correlations controlled for age, sex, education, cortical thickness, and MTsat in the corpus callosum, a region we previously used to demonstrate specificity (Turner et al., 2024). For longitudinal analyses, the APCs for cortical thickness and MTsat in the corpus callosum replaced the single time point values. Partial correlations were also conducted between LTDs and measures of AD risk (APOE4) and pathology (PET tau and amyloid burden). Linear mixed effects models were used to further examine the association between LTDs and longitudinal changes in MTsat across cortical ROIs. Main predictors included LTDs and elapsed time in months between timepoints. Covariates included age, sex, education,

MTsat in the corpus callosum, and cortical thickness. Given that linear mixed-effects models are robust to missing data, the full sample of 137 individuals was used in this model, with the same outlier data points coded as N/As.

Hierarchical regression was then conducted to determine if MTsat is a more robust predictor of task performance than cortical thickness in each ROI. Level one included demographic variables (age, sex, education). Level two included values for cortical thickness and MTsat in the corpus callosum from time point two. Finally, level three included MTsat values from time point two.

As a final step, we used constrained dominance analysis (Azen & Budescu, 2003), to derive the percent relative importance of each core region in predicting foraging performance. Each core region's APC and MTsat values from time point 2 were residualized for the control variables (age, education, sex, cortical thickness and MTsat in the corpus callosum) and each variable's contribution to the overall variance explained was assessed.

Results

MTsat and cortical thickness values for both timepoints and their APCs are reported in Table 2. Before addressing our core brain and behavioral hypotheses, we first examined the relationship between MTsat in each cortical region and age. Only the OFC showed a relationship with age at a single timepoint ($r = -0.37$, $p < 0.0001$) and no cortical region showed a relationship between age and APC. Next, we built on our earlier cross sectional finding of age-related decline in MTsat within LC to show evidence of longitudinal decline between data collection waves 1 and 2 ($r = -0.23$, $p < 0.05$). To examine microstructural

relationships within the explore-exploit ‘circuit,’ correlations between LC and cortical ROIs were calculated. Significant correlations were observed with OFC ($r = 0.41, p < 0.0001$), FPC ($r = 0.19, p < 0.05$), rMFG ($r = 0.43, p < 0.0001$), and dACC ($r = 0.21, p < 0.05$). There was no correlation with LO, our control region ($r = 0.08, p = 0.4$), suggesting that these associations were specific to the explore-exploit regions.

Mean MTsat and Cortical Thickness Values at Each Timepoint and APC

ROIs	MTsat TP1	MTsat TP2	MTsat APC	Cortical Thick- ness TP1	Cortical Thick- ness TP2	Cortical Thick- ness APC
OFC	1.38 (0.1)	1.34 (0.1)	-0.83 (2.0)	2.3 (0.09)	2.3 (0.08)	-0.30 (0.6)
FPC	1.28 (0.1)	1.27 (0.1)	-0.12 (4.3)	2.6 (0.13)	2.6 (0.13)	-0.05 (0.98)
rMFG	0.826 (0.04)	0.824 (0.04)	-0.13 (1.8)	2.3 (0.07)	2.3 (0.07)	-0.16 (0.57)
dACC	0.79 (0.04)	0.78 (0.04)	-0.39 (2.3)	2.3 (0.15)	2.3 (0.15)	-0.08 (0.58)
LO	0.86 (0.04)	0.87 (0.04)	0.33 (1.9)	2.2 (0.09)	2.2 (0.09)	-0.09 (0.80)

Table 2: TP = time point, APC = annualized percent change.

Cortical microstructural integrity and explore-exploit bias

We examined the relationship between each participant's LTD and MTsat values in each core cortical region. Consistent with predictions, lower MTsat values in the OFC ($pr(102) = 0.23, p < 0.05$), FPC ($pr(102) = 0.3, p < 0.01$), and rMFG ($pr(102) = 0.28, p < 0.01$) were associated with a bias towards exploitation on the berry foraging task (Figure 3). We did not observe this same relationship in the dACC or in the control region. Longitudinal declines in MTsat APC in the OFC ($pr(102) = 0.23, p < 0.05$), FPC ($pr(102) = 0.1, p < 0.05$), and rMFG ($pr(102) = 0.25, p < 0.01$), were also associated with a bias towards exploitation (Figure 4). No associations were observed in the dACC or the control region (OCC).

Cross-Sectional Correlations Between Cortical MTsat and Foraging

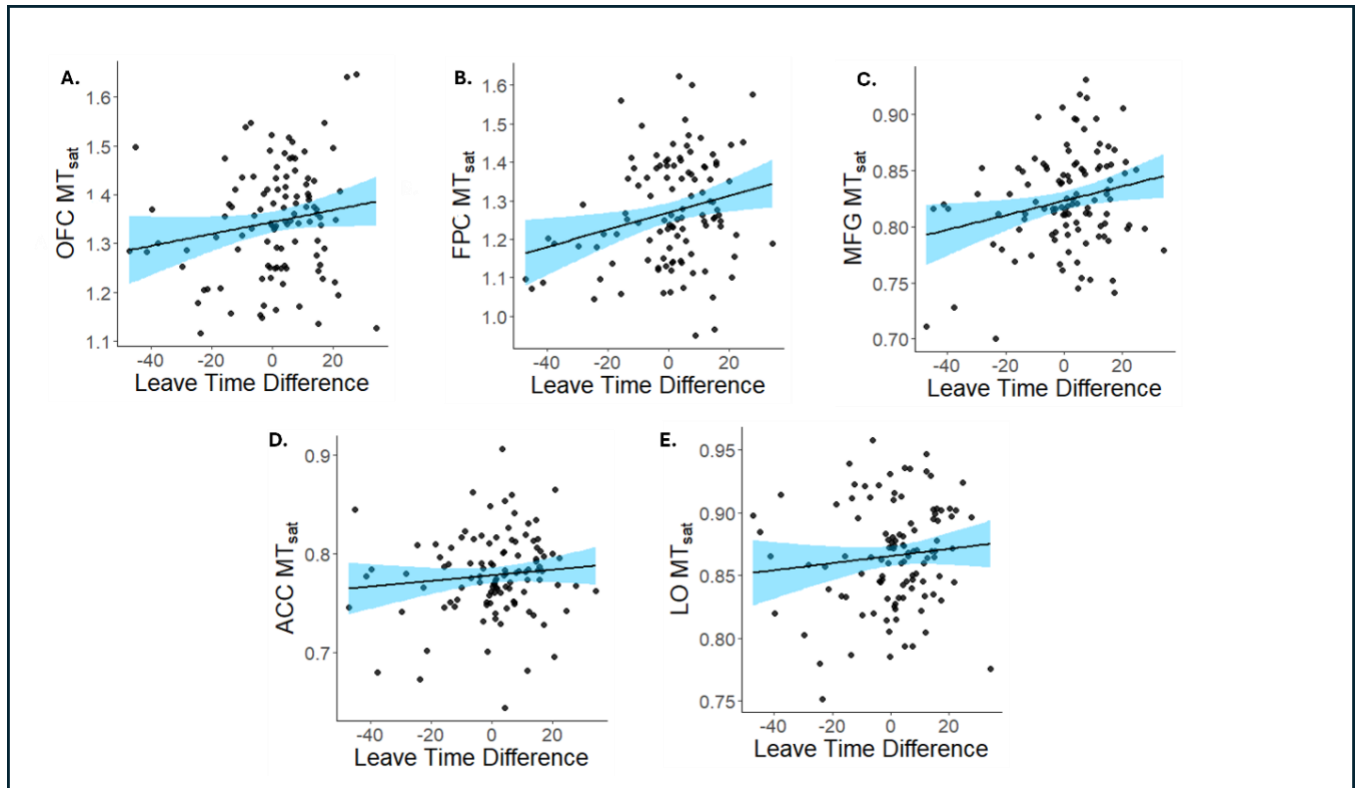


Figure 3: Panels A-E: Correlation plots for MTsat at time point 2 in explore-exploit regions (A-D) and a cortical control region (LO, Panel E) with exploration vs. exploitation (LTD). LTD values above 0 indicate an exploration bias while values below 0 indicate an exploitation bias. mOFC = medial orbitofrontal cortex, MFG = rostral middle frontal gyrus, FPC = frontopolar cortex, dACC = dorsal anterior cingulate cortex, LO = lateral occipital cortex.

Longitudinal Correlations Between Cortical MTsat and Foraging

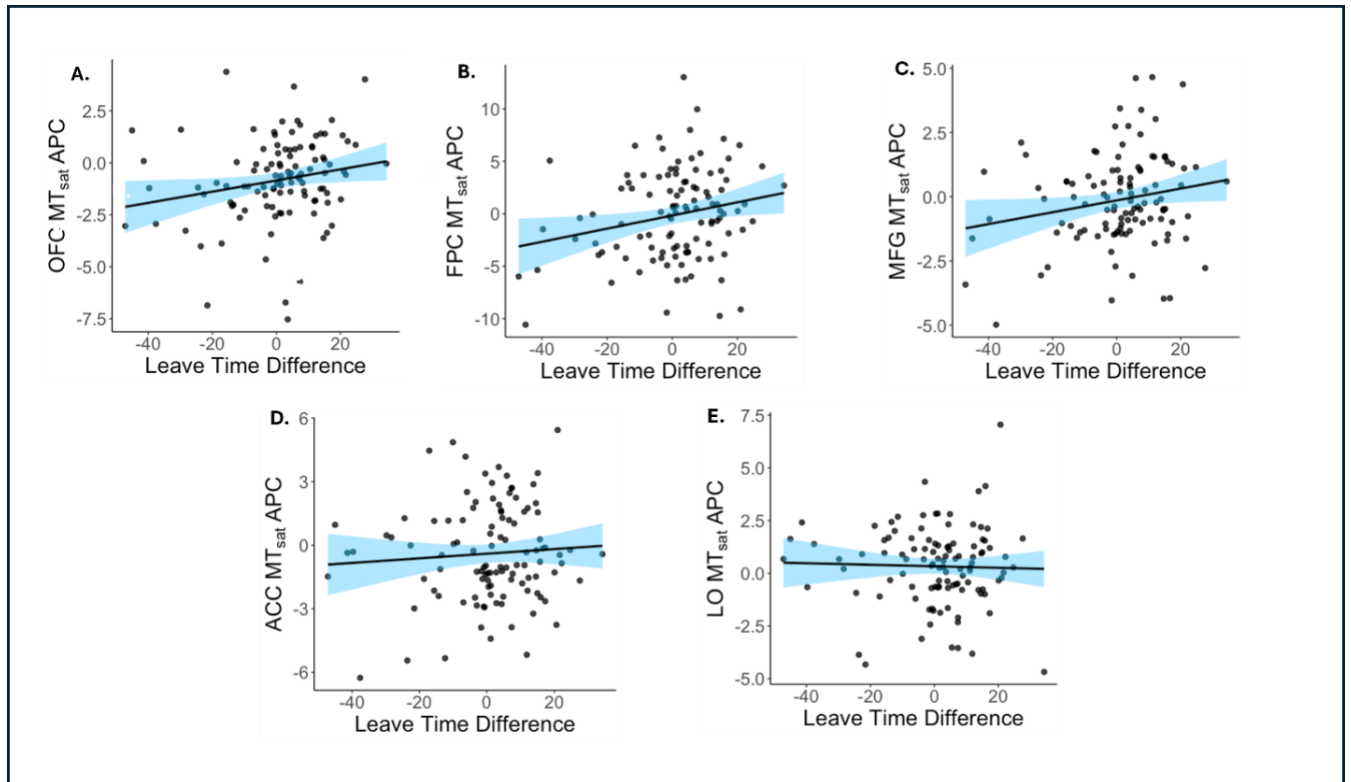


Figure 4: Panels A-E: Correlation plots for MTsat APC in explore-exploit regions (A-D) and a cortical control region (LO, Panel E) with exploration vs. exploitation (LTD). LTD values above 0 indicate an exploration bias while values below 0 indicate an exploitation bias. mOFC = medial orbitofrontal cortex, MFG = rostral middle frontal gyrus, FPC = frontopolar cortex, dACC = dorsal anterior cingulate cortex, LO = lateral occipital cortex.

To further test if an individual's LTD moderates longitudinal changes in MTsat, linear mixed-effects models were conducted separately for each region. Each model included elapsed time between sessions (months), LTD, and their interaction as predictors, along with covariates for age, sex, education, corpus callosum MTsat, and cortical thickness. Significant LTD $\times$ Time interactions were observed in the FPC ($\beta = -0.0087$, $p = .008$), OFC ($\beta = -0.0061$, $p = .002$), and rMFG ($\beta = -0.0058$, $p = .030$), indicating that individuals with an exploitation bias exhibited decreases in MTsat in these regions over time, while individuals with an exploration bias exhibited increases in MTsat in these regions over time (Table 3, Figure 5). The LTD $\times$ Time interaction was not significant in the dACC ($\beta = -0.0018$, $p = .566$) or the control occipital region ($\beta = -0.0007$, $p = .802$), suggesting regional specificity of the observed effects. Notably, there were no significant main effects of LTD at baseline in any region, consistent with the interpretation that foraging bias moderates structural change over time, rather than baseline differences in cortical structure.

Regression Results by Region

Predictor	FPC	OFC	rMFG	dACC	OCC
MU × Time	0.1419 ** [0.0387, 0.2451]	0.0985 ** [0.0379, 0.1591]	0.0936 * [0.0102, 0.1770]	0.0286 [-0.0686, 0.1258]	0.0118 [-0.0802, 0.1037]
MU	0.0717 [-0.0530, 0.1964]	0.0374 [-0.0868, 0.1616]	0.1183 [-0.0157, 0.2523]	0.0515 [-0.0772, 0.1802]	0.0639 [-0.0699, 0.1978]
Time	0.0441 [-0.0660, 0.1543]	-0.0706 * [-0.1392, -0.0020]	0.0784 . [-0.0127, 0.1696]	0.0137 [-0.0906, 0.1180]	0.0842 . [-0.0150, 0.1835]
Age	-0.1031 [-0.2321, 0.0259]	-0.2344 *** [-0.3616, -0.1073]	-0.0770 [-0.2179, 0.0640]	0.0512 [-0.0839, 0.1863]	-0.1658 * [-0.3060, -0.0255]

Table 3: Standardized beta weights (β) and 95% confidence intervals from linear mixed-effects models predicting MTsat from LTD, time, and their interaction. Each model includes age, education, gender, corpus callosum MTsat, and cortical thickness (additional covariates not shown for brevity). * $p < .05$, ** $p < .01$, *** $p < .001$.

Interactions Between Foraging and Time on MTsat in each Cortical Region

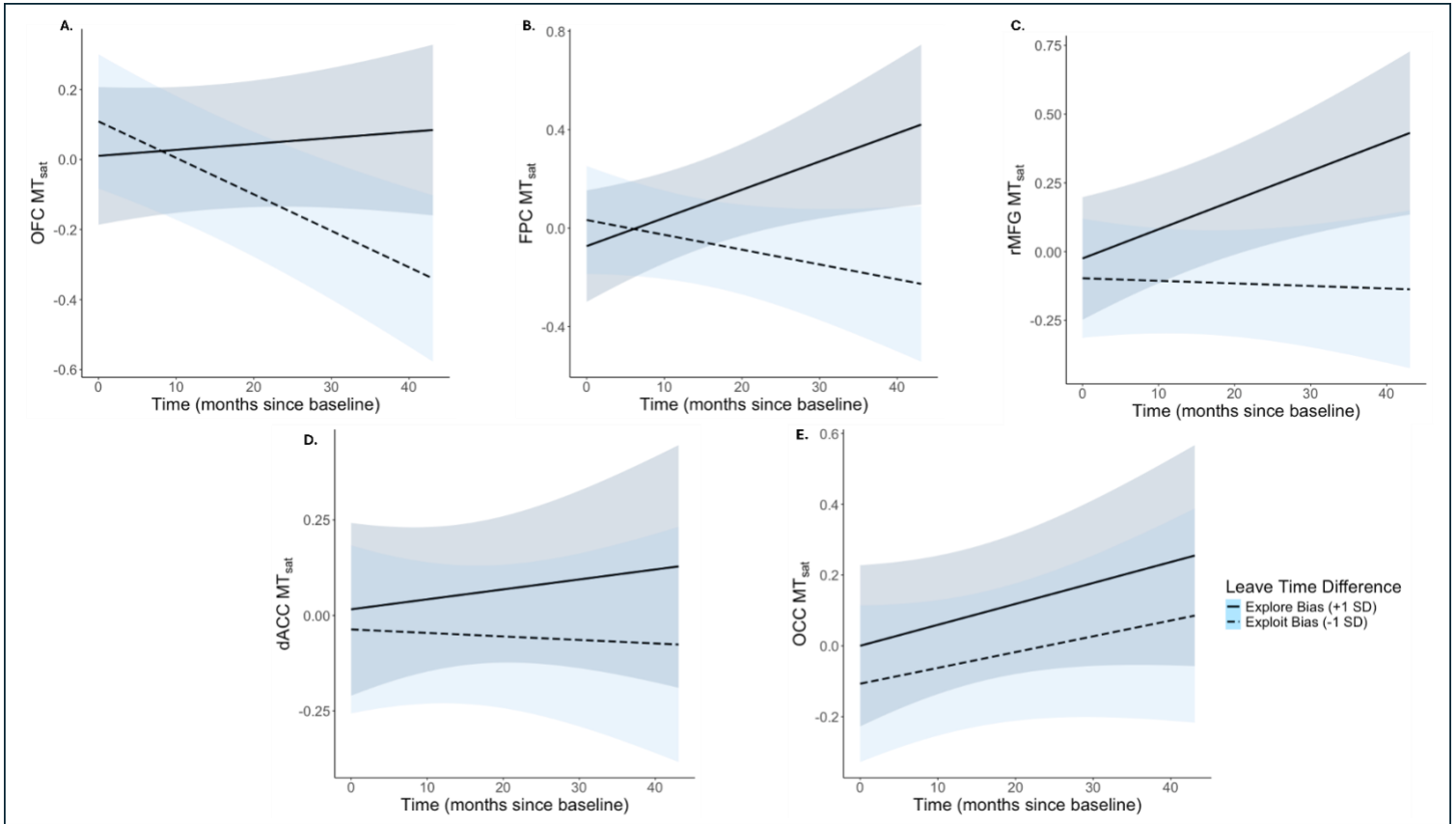


Figure 5: Panels A-E: Interaction plots depicting the relationship between time and MTsat in explore-exploit regions (A-D) and a cortical control region (LO, Panel E). The slopes represent the association between time and MTsat when biased towards exploration (+1 SD LTD) and exploitation (-1 SD LTD). mOFC = medial orbitofrontal cortex, rMFG = rostral middle frontal gyrus, FPC = frontopolar cortex, dACC = dorsal anterior cingulate cortex, OCC = lateral occipital cortex.

Next, constrained dominance analysis was conducted as an exploratory, data-driven approach to assess the overall importance of each region in predicting explore-exploit bias.

We compared both longitudinal and cross-sectional models to determine whether a single time point of data is sufficient to capture the relationship between structural integrity and behavior. The LC was also included to contrast subcortical versus cortical predictors. For each model, the percentage of relative importance (PRI) was calculated. Results showed that the LC MTsat acquired at the time the foraging task was administered was the most dominant predictor of foraging bias, followed by the FPC at the same timepoint. Consistent with predictions, the FPC was the strongest cortical predictor, showing two times the PRI of the OFC and rMFG. Relative contributions of all predictors are reported in Table 4.

Constrained Dominance Analysis

Region	General	Rank	PRI
OFC MT	0.03	3	10.2
FPC MT	0.05	2	20.4
MFG MT	0.02	4	10
ACC MT	0.005	10	2
LC MT	0.07	1	27.6
OFC MT APC	0.02	7	7.1
FPC MT APC	0.02	6	7.5
MFG MT APC	0.02	5	9.1
ACC MT APC	0.01	8	3.1
LC MT APC	0.01	9	3.1

Table 4: Percent relative importance (PRI) was computed for MTsat (MT) in each region and its annualized percent change (APC).

Macro- vs. microstructural predictors of explore-exploit decision-making

To examine whether our measure of cortical microstructure (MTsat) accounted for greater variance in foraging performance than standard macrostructural measures (cortical thickness), we conducted a hierarchical regression analysis for each region of interest: OFC, rMFG, FPC, and dACC. Cortical thickness is a widely used measure of brain structural integrity in aging research (Frangou et al., 2022) so we first controlled for thickness in each model and then tested whether MTsat added explanatory power. Our results followed a consistent regional pattern: the addition of MTsat significantly increased the variance explained in the OFC, rMFG, FPC, but not the dACC (Table 5). These findings highlight the added value of MTsat as a predictor of behavior beyond standard macrostructural measures.

Hierarchical Regression Examining Demographic Variables, Cortical Thickness, and MTsat

	Dependent Variables (DVs)			
	OFC	FPC	rMFG	dACC
Level 1				
Age	0.13 [−0.08, 0.34]	0.04 [−0.16, 0.23]	0.05 [−0.15, 0.25]	0.03 [−0.17, 0.24]
Education	−0.07 [−0.27, 0.12]	−0.13 [−0.32, 0.06]	−0.09 [−0.28, 0.09]	−0.06 [−0.26, 0.13]
Sex	−0.07 [−0.27, 0.12]	−0.12 [−0.31, 0.07]	−0.09 [−0.28, 0.10]	−0.04 [−0.24, 0.16]
R^2	.006	.006	.006	.006
F	.215	.215	.215	.215
Level 2				
Cortical Thickness	0.07 [−0.12, 0.27]	0.21 [0.02, 0.41]	0.08 [−0.11, 0.27]	−0.01 [−0.22, 0.19]
CC MTsat	−0.12 [−0.36, 0.12]	−0.07 [−0.28, 0.13]	−0.15 [−0.39, 0.08]	−0.01 [−0.24, 0.21]
R^2	.01	.12	.03	.007
ΔF	.19	1.42	.34	.07
ΔR^2	.004	.114	.024	.001
Level 3				
MTsat	0.29 [0.04, 0.54]	0.33 [0.13, 0.54]	0.34 [0.11, 0.57]	0.11 [−0.10, 0.33]
R^2	.06	.12	.09	.02
ΔF	5.45*	10.22**	8.48**	1.10
ΔR^2	.050	.000	.060	.013

Table 5: All standardized regression coefficients (β) are from the full model (level 3).

Level 1: demographics; Level 2: control variables; Level 3: MTsat at TP2.

Associations with AD Risk and Pathology

Partial correlations were conducted between the LTD parameter and APOE4 status, as well as PET-derived amyloid and tau burden. Contrary to our predictions, we did not observe any associations between foraging bias and APOE4 status ($r = 0.08$, $p = 0.4$), general amyloid load ($r = -0.12$, $p = 0.25$), or tau burden weighted across regions implicated in AD ($r = -0.12$, $p = 0.2$). Additionally, no associations were observed with MTsat at a single timepoint, or APC in MTsat across our ROIs (all regions $p > 0.05$).

Discussion

We used a measure of microstructural integrity (MTsat) in a set of cortical regions implicated in explore-exploit decision-making and performance on a foraging task to examine whether differences within this neural circuit are associated with explore-exploit decision-making performance in older adults. Negative associations with age were observed for MTsat in LC and OFC, but not in FPC, rMFG, or dACC. Consistent with predictions, lower MTsat in mOFC, FPC, and rMFG was associated with a bias towards exploitation both cross-sectionally and longitudinally. Critically, these associations remained when controlling for cortical thickness, suggesting that measures of microstructural integrity may provide a more sensitive neural correlate of behaviour than standard macrostructural measures. Consistent with this idea, in a statistical comparison of MTsat and cortical thickness, MTsat in mOFC, FPC, and rMFG ROIs emerged as a more robust predictor of explore-exploit behavior compared to cortical thickness in these regions. In a direct comparison of neural predictors of foraging, the LC explained the most variance followed by the frontopolar cortex,

which was a significantly more robust predictor than the other cortical ROIs. Measures of AD risk and pathology did not show a relationship with foraging or MTsat in cortical brain regions.

Age relates to lower MTsat in LC and OFC

We observed divergent correlations between age and structural integrity of the LC and cortical regions. As predicted, the OFC and LC showed declines with age. However, the FPC, rMFG, and dACC showed no relationship. Previously, we reported a cross-sectional association between increasing age and reduced LC integrity (Turner et al., 2024). However, in our current longitudinal investigation, only the LC showed an association between age and changes in structural integrity, as measured by MTsat change between timepoints. These findings suggest that the LC and mOFC are particularly susceptible to age-related structural decline as indexed by MTsat. The LC, an early site of tauopathies in the brain (Mather & Harley, 2016), showed accelerated structural decline over the approximately three-year interval between the sessions. Similarly, the mOFC, a region known for vulnerability to age-related tissue loss and tauopathies (Resnick et al., 2007), exhibited a relationship between lower microstructural integrity and age cross-sectionally. Both regions are known to decline during healthy aging (Braak & Braak, 1996; Hammerer et al., 2018), and previous work from our laboratory has proposed that this decline may contribute to an age-related exploitation bias (Spreng & Turner, 2021). The lack of associations between FPC, rMFG, and dACC and age may be due to MTsat indexing individual differences in microstructural integrity, rather than age-related structural declines (see below).

MTsat in cortical brain regions is associated with an exploitation bias, both cross-sectionally and longitudinally

Consistent with our previous findings in LC, lower MTsat and a decline in MTsat over time in the mOFC, FPC, and rMFG were associated with an exploitation bias. Additionally, we observed that foraging bias moderated MTsat change such that individuals who exploited more while foraging showed decreasing MTsat over time, even when accounting for baseline differences in MTsat. Lower MTsat may impair each region's capacity to process explore-exploit computations via reduced myelination and overall declines in microstructural integrity. The cortical regions we examined demonstrate moderate structure-function coupling (Fotiadis et al., 2023) and undergo slow myelination throughout life, likely increasing their susceptibility to environmental influences and individual variability in cortical plasticity (Carradus et al., 2020; Vidal-Pineiro et al., 2016). Previous studies have shown that mOFC activation (including both vmPFC and OFC,) is involved in encoding reward magnitude and the relative value current decisions (Daw et al., 2006; Laureiro-Martinez et al., 2013). In fMRI studies, the mOFC is typically related to exploit decisions (Addicott et al., 2014; Blanchard & Gershman, 2018; Dezza et al., 2019; Chakroun et al., 2020). However, it also encodes information relevant for exploration during reinforcement learning (Hogeveen et al., 2022) and reflects value differences between chosen and unchosen options during foraging tasks (Kolling et al., 2012). Our findings suggest that decreased integrity in this region may distort patch utility estimates during foraging, leading to the undervaluation of unexplored patches and the overvaluation of the current patch. Furthermore, as previously noted, the mOFC transmits task relevant information to the LC,

and degradation of this circuit may result in sluggish noradrenergic signaling and reduced flexibility when shifting towards exploratory behavior.

The FPC plays a key role in exploration decisions by encoding the relative future value of options that indicate when to switch to exploration (Daw et al., 2006). The FPC may also initiate a switch towards exploration by recruiting regions in the frontoparietal control network that inhibit the previous behavioral response and begin a new action (Hogeveen et al., 2022). Importantly, the FPC promotes behavioral flexibility during voluntary choice (Boorman et al., 2009), a critical component of the berry foraging task. In this task, participants could freely enter and leave patches according to their preferences. This differs from prior research that employed a fixed choice paradigm (Kolling et al., 2012), as it allows participants to initiate exploratory decisions at any time. Reduced structural integrity in the FPC may hinder the ability to initiate exploration freely, leading to suboptimal patch residence times.

The rMFG is a key executive control region involved in working memory, which helps generate model-based predictions regarding when to explore (Wyatt et al., 2024, Hogeveen et al., 2022). Optimal foraging requires participants to monitor both the average reward rate of the environment and the current reward rate of the present patch (Charnov, 1976). Foraging places demands on both working memory and broader executive control processes (Ólafsdóttir et al., 2020), which are strongly associated with the rMFG (Amiez & Petrides., 2007; Owen et al., 1998). Reduced integrity may impair the ability to actively model reward rates (Mansouri et al., 2015; Samanez-Larkin & Knutson, 2015). It may also reduce the fronto-parietal control network's efficiency in initiating exploration (Mata & von Helversen,

2015) and weaken spatial working memory (Ren et al., 2019), making it more difficult to recall previously lucrative patch locations.

Contrary to our predictions, we found no relationship between dACC integrity and foraging behavior. Unlike the other regions we measured, the dACC exhibits weak structure-function coupling (Fotiadis et al., 2023), indicating that structural changes in this area may not relate to functional outcomes. Furthermore, the dACC was the only region studied composed of agranular cortical columns (von Economo, 1929). Although the specificity of MTsat at this microstructural level remains unclear, we suggest that this subtle difference in cortical composition may have contributed to the lack of observed associations with the foraging task in this region.

MTsat correlates across LC and explore-exploit cortical regions

We observed robust, and specific associations between the microstructural integrity of LC and prefrontal brain regions implicated in explore-exploit decision-making (Cohen et al., 2007). This finding provides *in vivo* evidence of a similar subcortical-cortical circuit in humans. A recent study using high-field 7 Tesla MRI reported both structural and functional connections between the LC and the cortical target regions identified here. Using *in vivo* tractography, the authors generated a structural connectome of LC projections, and resting-state functional connectivity was used to examine functional links between the LC and cortex (Liebe et al., 2022). The LC is thought to regulate attention by integrating these cortical inputs that signal task performance (Aston-Jones & Cohen, 2005). It then adaptively modifies behavior via noradrenergic signaling, enhancing exploration or optimizing

exploitation. Declines in the structural integrity of this circuit in older adulthood may lead to sluggish noradrenergic signaling and a reduced capacity to flexibly shift attention, resulting in sub-optimal decision-making performance (Spreng & Turner, 2021).

LC and FPC microstructure best predict foraging bias

Interestingly, dominance analysis revealed that LC integrity is the most robust predictor of an exploitation bias, surpassing the target cortical regions of interest. This result highlights the importance of the LC as a core node underlying explore-exploit neural computations. It also supports recent research suggesting that the LC dynamically shapes neuronal receptivity throughout the brain (Wainstein et al., 2022). It is also consistent with the broader observation that cortical activity is shaped by brainstem nuclei (Hansen et al., 2024). Following the LC, the FPC emerged as the second strongest predictor of an exploitation bias and the strongest predictor of the cortical regions. This finding supports evidence that the FPC is uniquely involved in exploration and goal-directed behavior (Mansouri et al., 2017).

Cortical microstructure outperforms standard structural measures

In this study, MTsat proved to be a stronger predictor of decision-making performance than cortical thickness. Cortical thickness has been shown to decline linearly across the lifespan, whereas myelin, as measured by MT-related metrics, declines following a quadratic trend, with increased variability observed in older age (Carradus et al., 2020). While speculative, increased inter-subject variability may reflect ongoing cortical plasticity and changes in structural networks (Monje, 2018; Mount & Monje, 2017; Almeida & Lyons, 2017),

which may track more closely with brain function, and behaviour. Age-related changes in MT have been linked to declines in learning performance (Steiger et al., 2016) as well as episodic and working memory (Dahl et al., 2022). Moreover, individual differences in MT have been associated with variations in metacognitive ability (Allen et al., 2017). In contrast, cortical thickness reflects a range of morphological features, including neuronal cell bodies, glial cells, and dendrites (la Fougere et al., 2011; Frangou et al., 2022).

As noted above, MT-related metrics primarily reflect myelin content in neural tissue (Khodanoich et al., 2017; Schmierer et al., 2007; Soustelle et al., 2019; Marchsner et al., 2023; Mancini et al., 2020). Additionally, MT has been shown to detect changes in myelination within grey matter regions (Draganski et al., 2011; Ziminski et al., 2023), with robust correlations observed between grey matter MT and the underlying white matter tracts (Underhill et al., 2011). MT in grey matter may be particularly sensitive to myelination in both local microcircuits and longer-range projections (Pan et al., 2020; Bonetto et al., 2021; Ziminski et al., 2023). Furthermore, neurons in cortical grey matter show variable myelination. Neurons in deeper cortical layers tend to have more myelin than those in superficial layers, and myelination profiles differ across neuronal cell types (Call & Bergles, 2021; Tomassy et al., 2014). Although the role of myelin in grey matter is not fully understood, it is thought to serve several key functions. In addition to accelerating the propagation of action potentials along axons, myelin may synchronize neuronal firing in local circuits, support the metabolic needs of fast-spiking neurons, and inhibit the growth of aberrant axons and synapses (Timmmler & Simons, 2019; Micheva et al., 2016). Collectively, this research suggests that various myelinated sources contribute to MTsat in cortical grey

matter, and that myelin content in grey matter plays a crucial role in brain function, making it a potentially more sensitive structural brain measure of behaviour.

Explore-exploit decision bias is not associated with AD risk or pathology

Finally, we did not observe any associations between AD risk, indexed by genetic phenotype, or pathology, as measured by PET-derived measures of tau and amyloid burden, and either foraging bias or cortical MTsat in our sample. We interpret this finding to suggest that, even though this study cohort is at elevated risk for AD, the observed associations between exploitation bias and changes in MTsat are not attributable to common AD risk markers but rather emerge as a function of typical aging. Given that individuals with AD show a bias towards exploitation and fail to exploit efficiently (Troger et al., 2019), future research comparing explore-exploit bias and task performance across healthy older adults and individuals with neurodegenerative disease will help to better map the trajectory from adaptive to maladaptive exploitation.

Conclusion and Future Directions

In sum, our study provides novel evidence that declines in the structural integrity of cortical regions comprising the explore-exploit ‘circuit,’ are linked to an exploitation bias in older adults. As a fundamental trade-off that governs daily decision-making, a bias towards exploitation may shift the landscape of cognition in older adulthood. Although exploitation is safe and rewarding, every decision favoring familiarity comes at the expense of acquiring new information and experiences. Understanding how changes in the neural architecture underlying these decisions contribute to biased decision-making is essential for creating

more fulsome models of cognition in older adulthood, ones that integrate both age-related gains and losses.

We also found compelling evidence that a measure of tissue microstructure (MTsat) is a stronger predictor of decision-making behavior than a standard macrostructural measure (cortical thickness). This underscores the potential of qMRI-derived MPM techniques to uncover novel brain-behavior associations. Due to the ease of acquisition and high reliability across different sites and time points (Weiskopf et al., 2013), MPM techniques, and associated metrics including MTsat, open novel opportunities for tracking subtle brain changes in typical development and disease as well as more subtle brain-behaviour associations, opening the way for uncovering new neural markers and mechanisms linking neural structure and function to cognition and action.

Future research examining how aging affects additional explore-exploit domains, such as reinforcement learning and information search, will be crucial for understanding decision-making in older adulthood. While these domains share key features, they also differ in the types of computations required to balance explore-exploit. For example, foraging has elements of decision-making under risk (Krain et al., 2006), since switching patches involves weighing the current reward rate against the cost of travel and the uncertainty of future rewards. In contrast, reinforcement learning and information search resemble decision-making under ambiguity (Krain et al., 2006), where the value of options must be inferred from experience because the underlying distributions are unknown. Across all explore-exploit paradigms, task environments can be made more or less rewarding, informative, or computationally demanding, by manipulating available resources, limiting

access to information, or increasing the number of choice options, bandits, or patches. These subtleties reflect different aspects of real-world decision-making and have only recently begun to receive attention in the literature, especially in the context of aging.

Additionally, given the heterogeneity of tasks and computational models the reliability and validity of explore-exploit as a construct, and of each domain, should also be examined. Identifying tasks that are reliable, valid, and best suited for detecting individual and group differences will be important for translating explore-exploit research into clinical applications. In parallel, factors that may influence explore-exploit behavior, such as openness to experience, curiosity, mood, motivation, and executive functioning, should also be examined to identify whether they contribute to individual differences in explore-exploit bias.

Finally, combining multimodal structural and functional neuroimaging across the lifespan with reliable and valid explore-exploit tasks will enhance our understanding of the neural regions involved in decision-making and may help detect early signs of pathological aging and neuropsychological disease. To this end, our meta-analytic work integrated explore-exploit with canonical brain networks and proposed a network-based hypothesis of explore-exploit (Wyatt et al., 2024), and our previous results in LC alongside the current cortical results build on that foundation by identifying a subcortical-cortical circuit that changes with age and relates to an exploitation bias. In particular, the involvement of the LC highlights the importance of researching small, understudied subcortical structures such as those in the isodendritic core (Theofilas et al., 2015), which play an important role in aging cognition and closely and dynamically interact with cortical regions (Wearn et al. 2024). In

the context of the Shifting Mental Mode Hypothesis, our findings offer a foundation for examining the neuroscience of cognitive aging through the lens of explore–exploit behavior and suggest that an age-related bias toward exploitation may be an important marker of both adaptive and maladaptive aging. This underscores the value of the explore–exploit paradigm as a window into the broader mechanisms that shape healthy and pathological trajectories of late life development.

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