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Altered delay discounting in neurodegeneration: insight into the underlying mechanisms and perspectives for clinical applications

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ABSTRACT

Steeper delay discounting (i.e., the extent to which future rewards are perceived as less valuable than immediate ones) has been proposed as a transdiagnostic process across different health conditions, in particular psychiatric disorders. Impulsive decision-making is a hallmark of different neurodegenerative conditions but little is known about delay discounting in the domain of neurodegenerative conditions. We reviewed studies on delay discounting in patients with Parkinson's disease (PD) and in patients with dementia (Alzheimer's disease / AD or frontotemporal dementia / FTD). We proposed that delay discounting could be an early marker of the neurodegenerative process. We developed the idea that altered delay discounting is associated with overlapping but distinct neurocognitive mechanisms across neurodegenerative diseases: dopaminergic-related disorders of reward processing in PD, memory/projection deficits due to medial temporal atrophy in AD, modified reward processing due to orbitofrontal atrophy in FTD. Neurodegeneration could provide a framework to decipher the neuropsychological mechanisms of value-based decision-making. Further, delay discounting could become a marker of interest in clinical practice, in particular for differential diagnosis.

1. Introduction

Delay discounting describes how much people discount future compared to immediate rewards. Understanding the mechanisms of delay discounting is of importance for a large number of health conditions as well as for broader personal life and societal outcomes (Peters and Büchel, 2011). The assessment of delay discounting requires the subject to choose between a smaller, immediate reward or a larger, delayed reward (see Box 1 for further details on the delay discounting task). Most people prefer sooner rather than later rewards (e.g., almost everybody would prefer 100 euros right now over 101 euros in 2 years). However, the discounting rate (i.e., the degree to which delayed rewards are discounted, often noted "k") varies widely between individuals and these individual differences in self-control are a significant predictor of a number of important life outcomes. In particular, delay discounting predicts risks of drug use, criminal conviction (Moffitt et al., 2011) and is related to individual differences in smoking, obesity and overweight (Amlung et al., 2016; Bickel et al., 1999; Mole et al., 2015; Price et al., 2013). Steeper discounting has been found in a number of psychiatric conditions, including depression, schizophrenia, and bipolar disorder and has therefore been proposed as a transdiagnostic marker of psychiatric disorders (Amlung et al., 2019). There is also a growing body of literature linking neurodegeneration to modified delay discounting but, until now, no effort has been made to summarize and integrate the findings of these studies systematically.

In this perspective, we suggest that delay discounting is altered by the neurodegenerative process and might constitute an early marker of neurodegeneration. Most of the studies which investigated the neural

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Box 1

The delay discounting task.

One of the first influential tasks assessing delay discounting to be described in the literature was by Kirby and colleagues in the late 1990 s (Kirby and Maraković, 1996). The Kirby's Delay-Discounting Questionnaire or Monetary Choice Questionnaire is a self-administered 27-item test. In the presented 27 two-choice options, the monetary values range from $11 to $80 and time intervals for the delayed option range from 7 to 186 days. The items are divided into three groups according to the size of the larger amount (small, medium, or large) but the value alternatives are presented in a random order.

Many other versions of the task, with several of the task parameters changing, have been used in the studies investigating patients with neurodegenerative diseases. The first parameters which have shown variation are part of the trials structure. Indeed, the number of trials as well as their order of presentation (most often random) are found to vary in the literature. Some studies chose to present fewer items than 27, for example seven (Boyle et al., 2012, 2013), to adapt the task to populations with neurological disorders who may suffer from distractibility and/or fatigability like Alzheimer's Disease patients. Others, on the other hand, chose the opposite and present many more, such as 54 (Al-Khaled et al., 2015) or even 210 options (Evens et al., 2015). Importantly, the shorter versions showed a high correlation with the more standard and longer versions (Kirby and Maraković, 1996) suggesting that the number of trials does not have a significant impact on results (Boyle et al., 2012). Other task parameters which show huge variability in the field are to do with the chosen trial parameters: absolute delayed reward magnitudes, relative differences between the two rewards and delays between reward options.

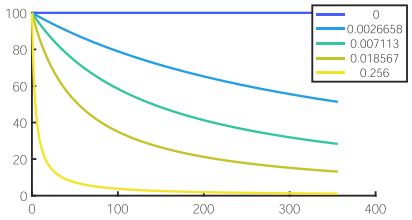
Studies investigating patients with neurodegenerative diseases also used rewards of different types. While most studies present monetary rewards, some offer food rewards (Bertoux et al., 2015; Aiello et al., 2019), rewards in the cultural and sport domains (Bertoux et al., 2015) or even offer to view erotic pictures (Girard et al., 2019). Moreover, the reward can be presented as a potentially real reward (whereby participants may receive their chosen reward option for one trial upon completion of the task) (e.g., Milenkova et al., 2011; Al-Khaled et al., 2015) or entirely hypothetical (e.g., Simioni et al., 2012). This may play an important role in terms of the ecological validity of these tasks.

We propose a short list of recommendations to make the delay discounting task incentive-compatible and ensure reliable results in patients: 1. the chosen trial parameters should cover a large spectrum of delays, SS and LL amounts, thus covering a large range of discounting parameters; 2. the participant should be clearly instructed and made aware that at least one of their choices (randomly selected) will determine the amount of reward they will actually receive and the delay to receive it; 3. as delay discounting is not domain general (Odum & Baumann, 2010) and may vary with the participant's level of interest in the specific type of reward, the type of reward used can impact results and this effect will depend on the studied condition (e.g., a patient with anorexia may show different discounting levels with monetary rewards and with food rewards). Therefore, best practice would be to systematically vary the types of rewards offered in a task, include money as a common standard reference, and try to match the reward to the most relevant domain in the condition of interest (to make altered discounting more salient).

Different outputs of the task.

Different outputs can be acquired from a delay discounting task. The main output is the *behavioral measure of delay discounting* which can be assessed from different measures, as described in the two next paragraphs. *Choice consistency* (i.e., the level of consistency of choices between options across the task) and *sensitivity to trial attributes* (i.e., how delay, delayed reward magnitude or relative value of two reward options impact subject's choice) are other possible outputs of the delay discounting task.

Typically, a participant's discounting curve may be calculated according to the following function: $V = A/(1 + kD)$, where V is the present subjective value of the delayed reward A at delay D, and k is the hyperbolic *rate of discounting*. Smaller k values indicate a lack of discounting and preference for delayed rewards while higher values indicate a strong discounting and a preference for immediate rewards. The graph shows different discounting curves (evolution of subjective value with time) corresponding to different values of k.



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Some studies of delay discounting in neurodegenerative disease populations have chosen to remove the assumptions about the shape of the discount function making the main output measure of the task the *impulsive choice ratio (ICR)*, i.e., the percent of choice of the smaller sooner reward or conversely the *percent of choices of larger later rewards (% LL)* (e.g., Beagle et al., 2020). This second type of measure of delay discounting has been found to strongly correlate with the hyperbolic discount rate (e.g., Lebreton et al., 2013).

correlates of delay discounting in healthy populations suggest a role of prefrontal and striatal areas (Bernhardt et al., 2014; Cooper et al., 2013; Ersner-Hershfield et al., 2009; Kable and Levy, 2015; Lebreton et al., 2013; Pehlivanova et al., 2018; van den Bos et al., 2014). Large-scale networks involving fronto-striatal circuits are often targeted in neurodegenerative conditions such as Parkinson's disease (PD), Alzheimer's disease (AD) or frontotemporal dementia (FTD) (Bertoux et al., 2015b; Seeley et al., 2009; Xu et al., 2016). Besides, poor capacities of decision-making are frequently observed in patients with neurodegenerative diseases (see (Gleichgerrcht et al., 2010) for a review). For these reasons, delay discounting is expected to be increased in neurodegenerative conditions but it is still unknown whether it could constitute a transdiagnostic marker, like for psychiatric disorders. Another question of interest concerns the evolution of delay discounting along the lifespan

A.

Database: Pubmed **Final search Date**: 2022.11 **Period:** 2003 -2023

Keywords:

Discounting keywords (Group 1)	delay discounting OR temporal discounting OR intertemporal choice
Neurodegeneration keywords (Group 2)	Alzheimer's Disease OR mild cognitive impairment OR frontotemporal dementia OR Parkinson disease OR dementia with Lewy bodies OR Huntington's disease OR progressive supranuclear palsy OR amyotrophic lateral sclerosis
Final Search String	(Group 1) AND (Group 2)

B.

Inclusion criteria:

1. studies including a delay discounting measure
2. participants include human adults with a neurodegenerative condition
3. original experimental articles published in a peer-reviewed journal
4. studies with full-text available in English
5. studies investigating: a cross-sectional or longitudinal comparison of delay discounting between groups of patients with a neurodegenerative condition (and controls) / a correlation between delay discounting and cognitive abilities / brain anatomical and functional correlates of delay discounting

Exclusion criteria:

1. studies including only measures of delay of gratification or probability discounting
2. studies recruiting only healthy participants or patients without a neurodegenerative condition
3. studies using animals as experimental subjects
4. review studies
5. studies focusing on the relationship between delay discounting and personality traits or religious orientation

C.

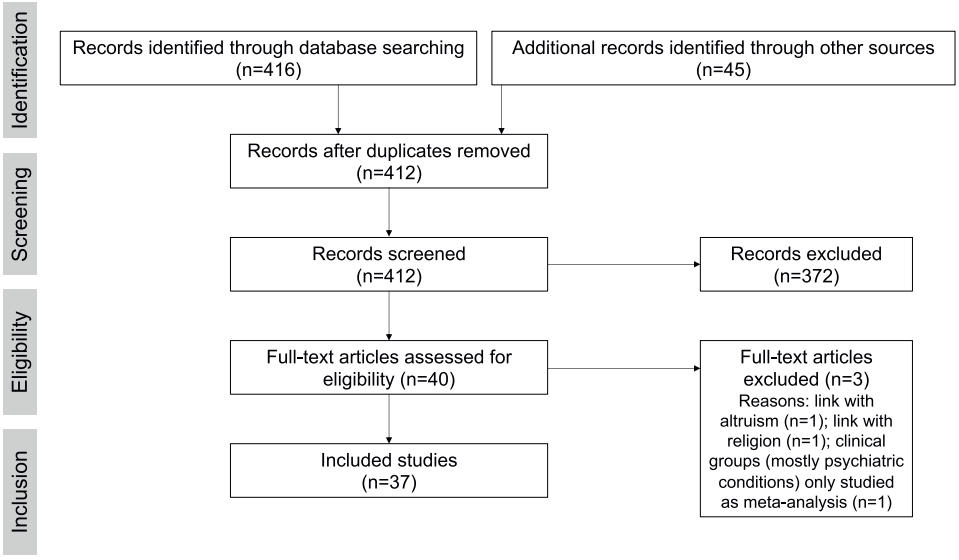

Fig. 1. Method used for the search and selection of studies investigating delay discounting in neurodegeneration. (A) Detailed search strategy in Pubmed; (B) Inclusion and exclusion criteria; (C) PRISMA flow diagram.

in relation with the neurodegeneration: is it gradually impaired with the evolution of cognitive decline and how early can this alteration be observed and measured?

Although altered delay discounting might be shared across neurodegenerative diseases, the combination of mechanisms causing this alteration can be specific to each condition. Self-control involves the complex coordination of several psychological and neural processes towards value-based decision-making (Berkman et al., 2017); thus, altered self-control and increased impatience (or increased discounting) can be related to distinct clinical and neuropathological features across neurodegenerative conditions. We suggest that investigating the specific links between each condition and altered discounting is of great interest to both the theoretical field of decision-making and the applied domain of clinical practice. For a better understanding of complex

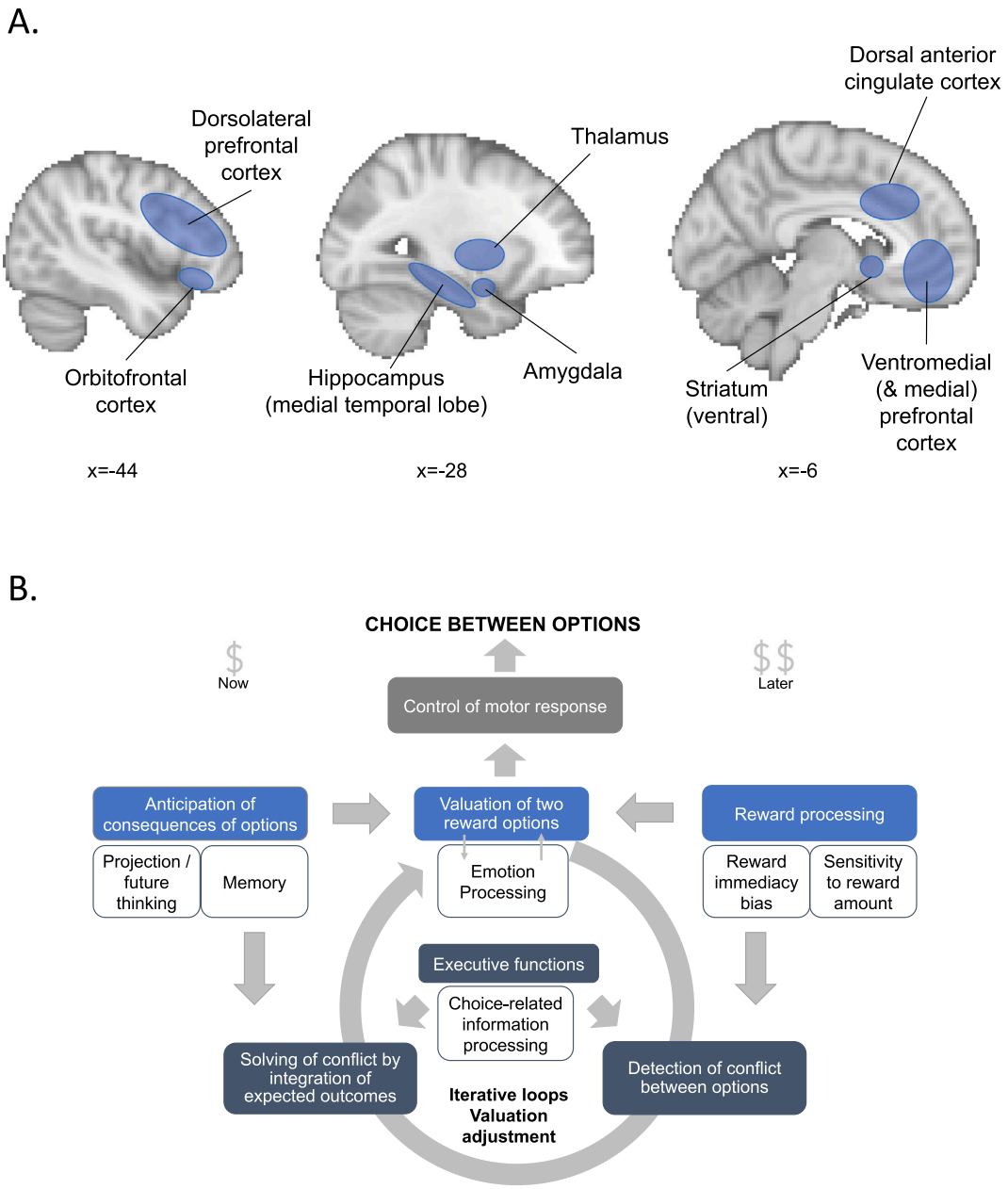

Fig. 2. Theoretical mechanisms of delay discounting. (A) Main brain regions assumed to be involved in delay discounting according to empirical findings in healthy subjects; (B) Neurocognitive model of the functional systems involved in choosing between the SS and LL options in a delay discounting task.

decision-making, it is necessary to unravel its underlying mechanisms, aside from mere associations with brain areas established exclusively by imaging studies of healthy individuals. By informing us about the patterns of altered delay discounting associated with specific anatomical and cognitive impairments, exploring delay discounting in neurodegenerative diseases has a great potential to help decipher the neuroanatomical and neuropsychological bases of intertemporal choices. Further, by providing insight into the causal effects of dopaminergic medication, investigating delay discounting in PD patients allows us to better understand the relationship between dopamine and intertemporal preferences. Regarding implications for clinical practice, identifying the specific changes responsible for modified delay discounting in each condition could help us understand the specificities of impulsivity associated with neurodegenerative diseases towards better prevention and care. More generally, the use of cognitive computerized tests with computational modeling of behavior (possibly combined with neuroimaging) is a promising route towards neurobiologically grounded diagnosis, personalized treatments as well as better mechanistic understanding of their therapeutic effects, in neurological conditions like in psychiatric conditions (Nour et al., 2022).

Here, we conducted a systematic review of studies on delay discounting in neurodegenerative diseases following the guidelines of preferred reporting items for systematic review and meta-analysis (PRISMA). We provided the context and objectives of the review, we described sources, eligibility criteria, and selection process of studies included in the review and we detailed our main variables of interest (see "Different outputs of the task" in Box 1). We used a list of key words related to delay discounting and neurodegeneration (delay discounting, temporal discounting, intertemporal choice, Alzheimer's Disease, mild cognitive impairment, frontotemporal dementia, Parkinson's disease, dementia with Lewy bodies, Huntington's disease, progressive supranuclear palsy, amyotrophic lateral sclerosis) in several databases, and we selected 37 studies based on pre-defined inclusion and exclusion criteria (see all methodological details in Fig. 1). Delay discounting

might be an important feature across all or most neurodegenerative diseases, but here we focused on the most frequent ones, in which delay discounting was sufficiently investigated. We found 23 studies involving patients with Parkinson's disease (PD) and 14 with patients within the Alzheimer's disease (AD) or frontotemporal dementia (FTD) spectrum. Although PD and AD/FTD dementias are caused by different pathological mechanisms, these conditions present partially overlapping cognitive and behavioral symptoms (e.g., executive dysfunctions) as well as partially overlapping atrophy patterns (involvement of fronto-striatal regions), which may contribute to a common feature of altered delay discounting across these diseases.

2. Delay discounting across the lifespan in healthy populations

Before delving into the neuropathological and neurocognitive changes related to altered delay discounting in neurodegenerative diseases, this section presents different factors impacting discounting in healthy subjects, in particular socio-demographic factors such as age as well as cognitive and neural characteristics. Moreover, this section addresses the following question: could altered delay discounting be used as an early marker of cognitive decline and further, as a predictor of neurodegeneration in older age?

2.1. Socio-demographic factors impacting delay discounting

One of the most studied demographic factors impacting delay discounting is age. Several theoretical frameworks propose different explanations for the effect of age. For instance, the theory of "limited time horizon" (e.g., (Carstensen, 2006)) suggests that discounting increases with age due to a reduction of the perceived probability of future reward (because of limited time horizon). Another point of view assumes that delay discounting decreases with age, particularly between adolescence/young adulthood and middle-age, as a consequence of a gradually decreasing reward sensitivity and increasing cognitive control (e.g., (Duckworth and Steinberg, 2015)). Combining these two frameworks, one could hypothesize a U-shaped relationship between age and delay discounting (decrease from adolescence to adulthood and increase from middle-age to older age). A recent meta-analysis (Seaman et al., 2020), including 37 cross-sectional studies with a total number of more than one hundred thousand adult participants, explored age-related effects on behavioral measures of delay discounting. In contradiction with the aforementioned hypotheses, this meta-analysis found no relation between age and temporal discounting. Results suggested that younger (approx. 18–35 years), middle-aged, and older (approx. 65–85 years) adults showed similar preferences for smaller, sooner over larger, later rewards. However, this conclusion was limited by the fact that the socioeconomic status was not considered as a moderating factor. In particular, a lower education level (potentially associated with lower parental income) might be associated with a lower cognitive development and lower decrease in discounting from adolescence to adulthood; more education and income may be related to lower increases in discounting from adulthood to older age owing to better cognitive reserve (see more details on the evidenced impact of education and income on discounting in the next paragraph). Thus, the absence of control for the education and income variables may have blurred the expected U-shape relationship between age and discounting.

Aside from age, other socio-demographic factors such as gender, education, income, and intelligence may also be related to delay discounting, potentially interacting with the effect of age. A meta-analysis of 33 studies by Silverman (Silverman, 2003) found that women discounted delayed rewards less steeply than men. However, the gender differences were small and detectable only by some measures of delay discounting. Moreover, several studies in different cultures observed that more educated individuals and individuals with higher income levels had substantially lower discounting rates (e.g., (Green et al., 1996; Harrison and McKay, 2012; Kirby et al., 2002; Reimers et al., 2009)). There is also clear evidence from multiple studies that higher intelligence (measured by IQ) is associated with lower delay discounting (see (Shamosh et al., 2008) for a meta-analysis) even after taking into account other variables, including socio-economic indicators (de Wit et al., 2007). Therefore, from a clinical point of view, the assessment of delay discounting as a potential indicator of cognitive decline should preferably take into account a patient's age, gender, and socio-economic status (education and income in particular).

2.2. Cognitive and neural bases of delay discounting

Delay discounting is a complex behaviour which most likely results from an interaction between different cognitive functions and brain areas. As suggested by Frost and McNaughton's model elaborated from empirical finding, several neurocognitive functions are involved in delay discounting, from the conversion of sensory signals into object representations until the final motor response to obtain the target gain (Frost and McNaughton, 2017). These cognitive functions include: 1. the processing of subjective reward values; 2. the anticipation of consequences of alternative options, involving memory functions; 3. the comparison between potentially conflicting options (considering the delay to obtain them) and final decision-making, requiring executive functions (information processing, inhibitory/attentional control).

A growing number of studies has investigated the neural correlates of delay discounting in healthy populations, using both structural and functional neuroimaging (Bernhardt et al., 2014; Cooper et al., 2013; Ersner-Hershfield et al., 2009; Kable and Levy, 2015; Kim et al., 2012; Lebreton et al., 2013; McClure et al., 2004; Pehlivanova et al., 2018; van den Bos et al., 2014). Fig. 2A shows the main brain areas involved in delay discounting according to observations in healthy subjects (Frost and McNaughton, 2017; Lempert et al., 2019; Peters and Büchel, 2011). At least three neural systems play a role in choices between smaller sooner and larger later rewards: the valuation and reward system (comprising the ventral striatum and ventromedial prefrontal cortex), the executive control system (including the dorsolateral prefrontal cortex), the memory and prospection system (including the hippocampus and medial temporal lobe) (Lempert et al., 2019). Very recent findings relative to an fMRI-based brain-marker of delay discounting (i.e., a whole-brain distributed pattern of functional brain activity that predicts individual differences in delay discounting) (Koban et al., 2021) provided further insight into the role of these functional networks in delay discounting. This study confirmed that higher activation of areas related to emotions, affect, valuation and reward processing, contributed to higher discounting (Koban et al., 2021). Moreover, among the functional networks found to predict discounting, areas related to conflict processing were very important contributors (Koban et al., 2021). These areas were especially recruited in cases requiring resolution of conflict: for long delays and small LL amounts in low discounters, for shorter delays and larger LL amounts in high discounters.

Relying on evidence of cognitive and neural mechanisms involved in delay discounting, we propose a neurocognitive model (shown in Fig. 2B) to explain how individuals make their decisions between the SS and LL options. This model will serve as a reference throughout the review to support theoretical considerations on the specific mechanisms involved in the alteration of delay discounting in PD, AD and FTD. The model is based on the assumption that the final valuation of alternative options depends on both a process of motivational assessment (reward processing combined with anticipation of consequences of options) and an executive process of iterative valuation adjustment depending on the detection of conflict between options. The individual reward immediacy bias (i.e., the unconditional preference for immediate rewards regardless of the amounts of the rewards) and sensitivity to reward amounts would contribute to determine a first estimation of the attractiveness of alternative options, complemented by a first anticipation of their consequences. The process of valuation would permanently interact with internal emotion processing and valuation iterative adjustment would

rely on the central role of higher-level executive functions, including: 1. the progressive integration of external choice-related information (delay and reward values) and 2. the inhibitory and attentional processes maintaining focus on optimized valuation (and avoiding to rush into a suboptimal solution). The valuation optimization process would start with the detection of a conflict between options and progress until the resolution of the detected conflict. Detecting conflict between options would depend in particular on an individual's reward immediacy bias and extreme levels of reward immediacy bias would tend to decrease the detection of conflict between options; with very high reward immediacy bias and tendency to overvalue the SS option, only extremely short delays with large LL amounts could become conflictual situations whereas with very low negative reward immediacy bias implying a consistent tendency to prefer the LL option, conflict might emerge only for extremely long delays combined with small LL amounts. After detecting conflict, the second step of the valuation adjustment loop would serve the purpose of conflict resolution by further integrating expected outcomes of options based on past experiences. This second step would involve autobiographical memory and capacity for projection in the future.

2.3. Delay discounting as an early marker of cognitive decline and predictor of disease in healthy older adults

Since delay discounting involves so many cognitive functions, it might be a useful tool for early detection of cognitive and functional decline in heathy older adults (approx. 65–85 years). Among older individuals without dementia, discounting rates were higher for individuals who reported a mental shortfall (Huffman et al., 2019) and for individuals with a lower global level of cognitive function objectively measured by a battery of 19 tests (Boyle et al., 2012). Moreover, a longitudinal study in a large sample of older adults (without dementia or MCI) found that a higher delay discounting rate at the baseline was associated with greater cognitive decline (measured by the same battery of 19 tests) in the three years follow-up, thus suggesting that delay discounting could be an early predictive marker of future cognitive decline (James et al., 2015). Of note, consistency in choices made across the delay discounting task may also serve as a more general marker of cognitive and functional decline (but this is not specific to the delay discounting task). In particular, delay discounting response consistency in older adults was found to account for significant additional variance in functional ability assessed by the instrumental activities of daily life (IADL) scale (Lindbergh et al., 2014a).

Among different cognitive functions, steeper delay discounting in older age has been more specifically related to memory deficits and to global decision-making impairments. In older adults aged from about 60 to 90, individuals showing higher delay discounting also presented lower performance on episodic and autobiographical memory functions (Lempert et al., 2020a, 2020b). Moreover, a cross-sectional study (Halfmann et al., 2013) found that among older adults, lower scores on the Iowa Gambling Task (IGT) were associated with higher discounting of future rewards. The IGT is one of the most traditional tests used to measure decision-making capacity under ambiguity and is assumed to be an indicator of dysfunctional orbitofrontal / medial prefrontal cortex (Bechara et al., 2000). In this test, participants can hypothetically either receive or lose different amounts of money when repeatedly choosing a card from one of 4 decks. Participants are instructed to try to maximize their gains. The amount of "loss-cards" differs per deck, leading to 'good' and 'bad' decks towards the objective of maximizing gain.

Interesting findings involving the assessment of delay discounting in old age suggest that this specific feature of decision-making could be an early predictor of lethal disease emergence even before the onset of symptoms. In a longitudinal cohort study including 406 older persons without dementia, delay discounting was associated with an increased risk of mortality during up to 5 years of follow-up (Boyle et al., 2013). According to this study, a person with the highest discount rate was about twice more likely to die over the study period compared to a person with the lowest discount. Further, the association of delay discounting with mortality persisted after adjustment for the level of global cognitive function, the burden of vascular risk factors and diseases, and an indicator of psychological well-being (i.e., purpose in life).

2.4. Delay discounting as an early predictor of neurodegenerative diseases?

The predictive capacity of delay discounting could be very useful in the context of neurodegenerative diseases. For an efficient tracking of neurodegeneration, one needs a variety of cognitive markers relative to all cognitive domains to make sure that early changes can be detected whatever the cognitive profile. The great potential of delay discounting hinges on its sensitivity to changes in several cognitive domains such as executive functions, valuation and reward processing. Testing episodic memory cannot be sufficient on its own either to make a diagnosis of AD or to track the evolution of patients. Moreover, episodic memory is not primarily impacted in all neurodegenerative conditions. For instance, in most FTD patients, behavioral and psychiatric symptoms, not memory disturbance, are the predominant initial symptoms (Shinagawa et al., 2006). The early detection of impairments in executive functioning is interesting as they occur in many neurodegenerative diseases including FTD (Rascovsky et al., 2011) and PD (Dirnberger and Jahanshahi, 2013). Even in AD, although episodic memory complaints are the most prominent, executive complaints have been shown to distinguish different stages and are therefore clinically relevant (Cacciamani et al., 2022). The reward system is also central to a lot of neurodegenerative diseases, in particular in PD (Costello et al., 2022), yet reliable tasks to assess its integrity in clinical neuropsychology are still lacking. Finally, if personality traits are associated with the risk of cognitive impairment in older adulthood (Crowe et al., 2006) potentially preceding the onset of a disease, delay discounting which has been proposed as a stable trait-like measure of impulsivity (Odum, 2011) might present an added value for the very early prediction of neurodegenerative disease.

In Alzheimer's disease patients for instance, we now know that neuropathological and brain changes appear many years before clear cognitive changes are detected (Dubois et al., 2014). Altered delay discounting may be a useful cognitive marker during the early phases of the disease. Indeed, it was observed that individuals with subjective cognitive decline (SCD; an at-risk state of Alzheimer's disease in which individuals subjectively experience cognitive decline even though their performance is normal on objective cognitive tests (Jessen et al., 2014)) showed reduced future-oriented choices during a functional magnetic resonance imaging (fMRI) task assessing delay discounting (Hu et al., 2017). The task contrasted trials with and without simultaneous episodic future imagination. This allowed to observe that future imagination, which increased future-oriented choices, was associated with increased activation in some brain areas (including medial frontal, insular and anterior cingulate cortices) only in healthy controls but not in participants with SCD. Thus, subtle neuronal network disruptions in SCD may be enough to modify delay discounting through a lack of modulation of choice behavior by episodic future imagination.

Further longitudinal follow-up studies are still needed to better estimate the predictive value of delay discounting in the context of neurodegeneration. In particular, aside from the detection of cognitive decline, the capacity of delay discounting to detect the pathophysiological changes related to the neurodegeneration process should be further explored. Using data from deceased individuals without clinical dementia and previously involved in studies on ageing, it was possible to show that the amyloid pathology, a pathologic hallmark of Alzheimer's disease, was associated with poor healthcare and financial decision making (assessed by the performance to answer questions requiring integration of information about health maintenance organization plans or mutual funds) (Kapasi et al., 2021). Thus, this study provided compelling evidence that decision making quality is sensitive to the

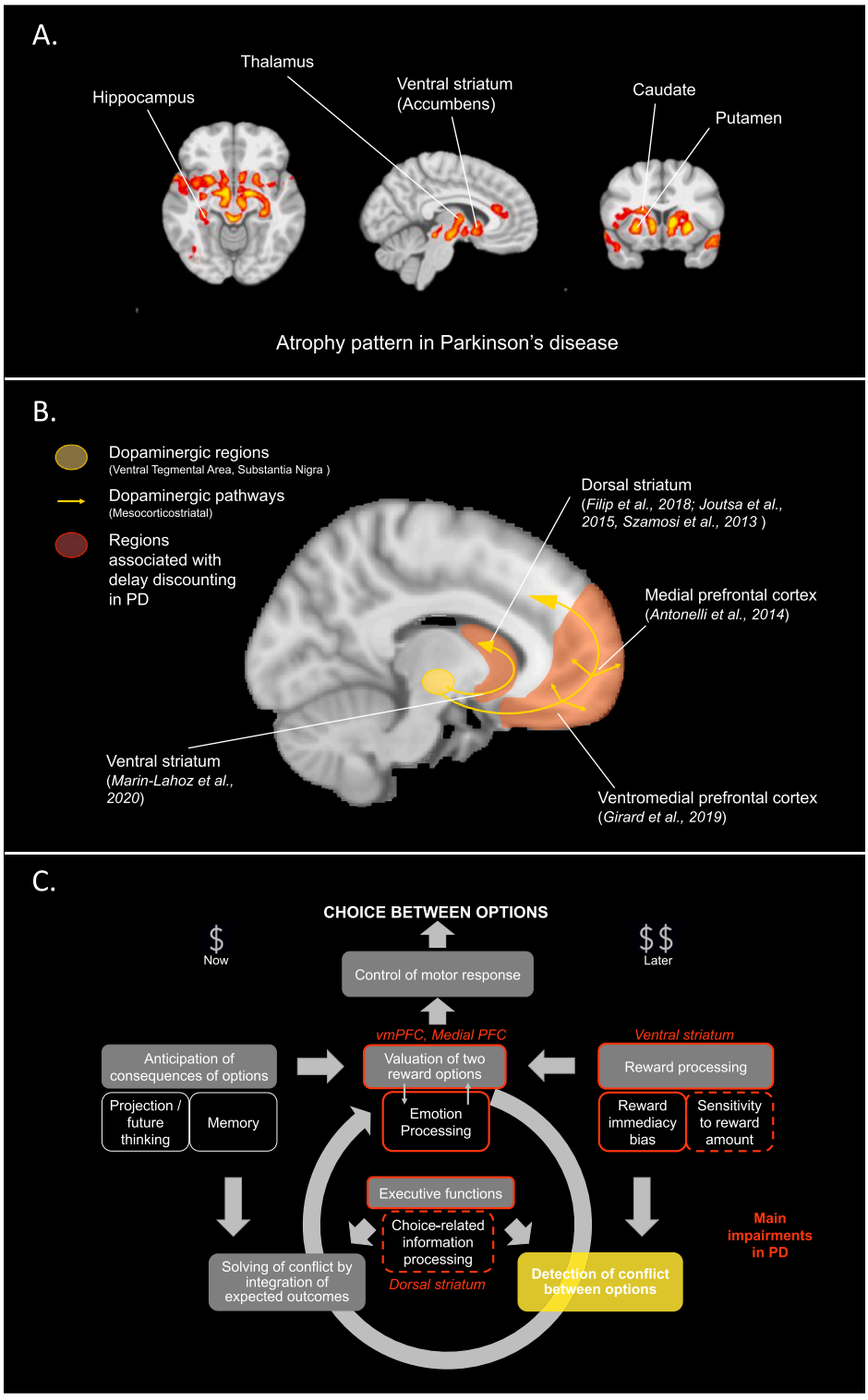

Fig. 3. Neuropathology and mechanisms of delay discounting in Parkinson's disease. (A) Atrophy distribution in early *de novo* Parkinson's disease (results from Zeighami et al., 2019); (B) Brain regions related to delay discounting in studies involving patients with Parkinson's disease; (C) Neurocognitive model explaining altered delay discounting in PD. Mechanisms evidenced to be disturbed in PD are circled in red (dotted line for PD with ICD). Brain regions shown to be involved in altered discounting in PD are in red.

earliest pathological changes of Alzheimer's disease. However, it is still unknown whether the amyloid pathology is associated with altered delay discounting specifically and the mechanisms potentially linking this pathology to steeper delay discounting would have to be investigated.

If delay discounting was to be used in clinical practice for early detection of neurodegenerative diseases, some psychometric criteria would also have to be further investigated. The delay discounting task has already been shown to fulfill reliability criteria required for neuropsychological tests. In particular, the test - re-test reliability has been verified by several studies (Anokhin et al., 2015; Harrison and McKay, 2012; Koban et al., 2021), suggesting that individual differences in delay discounting are rather stable over time. The next step for the adaptation to clinical practice would be to define cut-offs of delay discouting associated with neurodegenerative diseases. This would allow in particular to assess the accuracy (sensitivity and specificity) of delay discounting to detect neurodegeneration (i.e., classify patients with neurodegenerative disease vs controls). Since delay discounting is

Table 1
Studies assessing delay discounting in PD patients and their main results[a].

Reference	Populations						Manipulations[b]		Comparisons on delay discounting measure
	PD ICD- DRT-	PD ICD- DRT+	PD ICD+ DRT+	PD DBS- DRT+	PD DBS+ DRT+	HC	DRT ON vs OFF	DBS ON vs OFF	
Aiello et al. (2019)				N = 15	N = 15	N = 15	No	No	PD DBS+ = PD DBS- = HC
Al-Khaled et al. (2015)	N = 13	N = 24				N = 22	No	No	PD DRT- > PD DRT+ = HC
Antonelli et al. (2014)		N = 7					Yes	No	PD DRT "ON" > PD DRT "OFF" only for higher reward magnitudes
Averbeck et al. (2013)		N = 18	N = 18			N = 20	No	No	PD ICD+ > PD ICD- = HC
De Rezende Costa et al. (2016)	N = 25					N = 20	No	No	PD ICD- DRT- = HC
Evens et al. (2015)				N = 33	N = 33	N = 25	No	Yes	PD DBS+ > HC; PD DBS- = HC PD DBS "ON" = PD DBS "OFF"
Filip et al. (2018)		N = 13	N = 8			N = 28	No	No	PD ICD+ = PD ICD- = HC
Foerde et al. (2016)		N = 30				N = 20	Yes	No	PD DRT "ON" < PD DRT "OFF" = HC Sensitivity to delay: PD DRT "ON" < HC
Girard et al. (2019)		N = 14	N = 13			N = 14	Yes	No	PD ICD+ DRT "ON" < PD ICD- DRT "ON" (NB: LL reward = view erotic images for longer)
Hlavata et al. (2020)		N = 22	N = 15			N = 36	No	No	PD ICD+ = PD ICD- = HC
Housden et al. (2010)		N = 18	N = 18			N = 20	No	No	PD ICD+ > PD ICD- = HC
Izzo et al. (2020)		N = 41	N = 10			N = 42	No	No	PD ICD+ > PD ICD- ICD predicted by higher DD in PD
Joutsa et al. (2015)		N = 10	N = 10			N = 12	No	No	PD ICD+ = PD ICD- = HC
Leroi et al. (2013)		N = 55	N = 35			N = 20	Yes	No	PD ICD+ DRT "ON" > PD ICD- DRT "ON" PD ICD+ DRT "OFF" = PD ICD- DRT "OFF"
Marin-Lahoz et al. (2020)		N = 89					No	No	Correlation analyses (DD uncorrelated with other measures of impulsivity in PD)
Milenkova et al. (2011)		N = 17				N = 17	Yes	No	PD DRT "ON" = PD DRT "OFF" > HC
Nombela et al. (2014)		N = 30				N = 30	No	No	PD ICD- DRT+ = HC
Seinstra et al. (2016)					N = 30		Yes	Yes	PD DRT "ON" = PD DRT "OFF" PD DBS "ON" = PD DBS "OFF"
Seymour et al. (2016)					N = 22		No	Yes	PD DBS "ON" = PD DBS "OFF"
Simioni et al. (2012)		N = 23				N = 20	Yes	No	PD ICD- DRT+ = HC PD DRT "ON" = PD DRT "OFF" Consistency: DRT "ON" < DRT "OFF"
Szamosi et al. (2013)		N = 7				N = 10	No	No	PD ICD- DRT+ > HC
Terenzi et al. (2021)		N = 13	N = 15			N = 15	No	No	PD ICD+ > PD ICD- = HC (NB: tDCS did not lower DD in PD ICD+)
Voon et al. (2010)		N = 14	N = 14			N = 16	Yes	No	PD ICD+ = PD ICD- = HC PD ICD+ DRT "ON" > PD ICD+ DRT "OFF" PD ICD- DRT "ON" = PD ICD- DRT "OFF"

[a] Only the main results regarding comparisons on behavioral measures of delay discounting (or other outputs like sensitivity to trial attributes) are described here.
[b] Manipulations are acute short-term manipulations. ICD: Impulse Control Disorders; DRT: Dopamine Replacement Therapy; DBS: Deep Brain Stimulation (of subthalamic nucleus); + /-: with/without.

supposed to be a transdiagnostic marker across many health conditions (including psychiatric conditions), this measure is likely to be more sensitive than specific for the early detection of neurodegeneration. Moreover, before using it in clinical practice, the exact added value of delay discounting assessment to track neurodegeneration, in comparison to other neuropsychological measures, should be demonstrated.

3. Delay discounting in Parkinson's disease

After describing the main characteristics of PD condition, this section details results on the links observed between delay discounting and specific aspects of the disease (neuropathology, impulsivity symptoms and treatments) in order to decipher their respective roles in the alteration of delay discounting. The section ends with the description of implications regarding: 1. the theoretical neurocognitive mechanisms of modified delay discounting in PD and its specific relation to the dopaminergic system functioning; 2. the clinical value of the task in PD patients for the prevention of impulsivity symptoms.

3.1. Clinical-neuropathological hallmarks of PD

Parkinson's disease (PD) has long been considered as a mere movement disorder, but it is now generally acknowledged as a more complex condition affecting multiple motor, cognitive, and behavioral components. Of note, dementia can also affect some individuals with PD but in this review, PD condition refers to PD without dementia. Neuropsychiatric affections such as depression and apathy can be associated with PD, and impulsivity troubles including impulse control disorders may arise in about 15% of patients with PD (Cooney and Stacy, 2016). Impulse control disorders (e.g., pathological gambling or shopping, intermittent

explosive disorder, kleptomania, pyromania, trichotillomania) are defined by the World Health Organization as repeated acts that have no clear rational motivation, generally harm the person's own interests and those of other people, and are associated with impulses experienced by the person as uncontrollable. Dopamine deficiency is one of the neuropathological hallmarks of PD, which is targeted by dopaminergic treatments, and typical atrophy pattern mainly includes regions of the mesocorticolimbic dopaminergic system (in particular, basal ganglia and medial prefrontal cortex) and medial temporal lobe (Zeighami et al., 2019) (see Fig. 3A).

Several aspects of PD condition suggest a possible alteration of delay discounting. There is converging evidence supporting a role of the dopaminergic function in delay discounting (e.g., (Joutsa et al., 2015; Koffarnus et al., 2011; Sweitzer et al., 2013)). Thus, PD core neuropathology may alter delay discounting. PD treatments modulating dopaminergic function may also contribute to modifications of delay discounting. Among PD possible symptoms, impulse control disorders (ICD) (which manifest impulsive decision-making) may in particular be related to altered delay discounting.

All delay discounting studies in PD reviewed in this work to explore these hypotheses are summarized in Table 1, along with their main behavioral results. These studies evidenced specific brain regions related to delay discounting in PD, as shown in Fig. 3B.

3.2. Links between delay discounting and PD clinical features

Studies which explored altered delay discounting as a core feature of PD by recruiting drug-naïve PD patients (to avoid the interference of dopamine medication) found mixed results (Al-Khaled et al., 2015; de de de Rezende Costa et al., 2016). One study (Al-Khaled et al., 2015) found that unmedicated PD patients had a higher discounting rate than controls, but another one (de de de Rezende Costa et al., 2016) did not confirm this result. Besides, Szamosi et al. (Szamosi et al., 2013) analyzed delay discounting in seven pre-symptomatic patients, carriers of a mutation predisposing to PD, who later developed PD. Carriers of this mutation started to show elevated discounting rates (compared to controls) very soon after the onset of PD. Though this could be due to the effect of dopaminergic treatment, if it is due to the disease process itself, it suggests that delay discounting is not altered presymptomatically. Thus it probably could not be used as an early predictor of PD but maybe as an early marker of disease onset.

The mixed findings in patients with *de novo* PD might result from a probabilistic effect similar to what could be observed in the general population. However, studies investigating the relationship between delay discounting and atrophy of the striatum in PD (Marín-Lahoz et al., 2020; Szamosi et al., 2013) advocate for a role of PD neuropathology in altered discounting (see Fig. 3. B). In the study by Szamosi and colleagues, it was found that once subjects with a genetic predisposition had developed PD, they showed a significantly lower caudate volume compared to controls and there was a negative correlation between caudate volume and delay discounting for all reward magnitudes. In a much larger sample of PD patients, another study showed that higher discounting rates were related to lower grey matter volumes in the nucleus accumbens (ventral striatum) but only for low reward values (Marín-Lahoz et al., 2020).

Other aspects of PD symptomatology may predispose patients to discount more. Aside from impulse control disorders (which are detailed in the next section), impairments of valuation, reward processing, emotional processing, and executive dysfunction may contribute to alter delay discounting in PD. A very recent literature review (Costello et al., 2022) aimed to determine whether reward processing was impaired in PD patients; they concluded that patients on medication exhibited a small-to-medium impairment of reward processing compared to healthy controls, but greater impairments (especially option valuation and reward response vigor) were observed off dopaminergic medication. This suggests a role of PD core pathology in disturbances of reward processing. PD neuropathology also involves neural systems thought to be involved in emotional processing (i.e., the striato-thalamo-cortical circuits and the mesolimbic dopamine system that modulates their function) and emotional disturbances were indeed consistently observed in PD (Péron et al., 2012). Moreover, executive dysfunction can be present from the early stages of PD; it includes deficits in internal control of attention, planning, and inhibitory control which relate to pathology of the basal ganglia (Dirnberger and Jahanshahi, 2013).

3.3. Links between delay discounting and impulse control disorders in PD

Impulse control disorders (ICD) could be defined as "behavioural addictions" which are characterized by abnormalities in reward processing (Grant et al., 2014). In line with this assumption, Terenzi et al. (Terenzi et al., 2021) found higher reward wanting in PD patients with ICD and Averbeck et al. (Averbeck et al., 2013) put forward a general mechanism underlying ICD by using three different tasks including the delay discounting task: PD patients with ICD behaved as if they could not use the information provided within the experimental context to guide their actions towards obtaining future rewards. Thus, altered delay discounting might constitute one of the mechanisms fostering the emergence of ICD. Moreover, specific impairments of brain functioning in patients with ICD may modify their neural activity while choosing between an immediate and delayed reward option.

Higher discounting does not necessarily result in the emergence of ICD: some studies found either slightly increased (Al-Khaled et al., 2015; Nombela et al., 2014; Simioni et al., 2012) or considerably steeper (Milenkova et al., 2011) discounting rate in PD patients without ICD (compared to controls). Another question which arises is whether the emergence of ICD is systematically associated with an increase in delay discounting or not. Some results are consistent with the hypothesis of an association between ICD and elevated discounting, at least in PD patients (Housden et al., 2010; Izzo et al., 2020; Terenzi et al., 2021) but other studies (Filip et al., 2018; Hlavatá et al., 2019; Joutsa et al., 2015) did not evidence any significant difference in delay discounting between PD patients with and without ICD. The heterogeneity of results on delay discounting in PD patients with ICD might be a consequence of the heterogeneity of PD (Farrer, 2006; Lewis et al., 2005; van Balkom et al., 2016) and the influence of confounding variables, such as age, age at PD onset, depression, or dopaminergic status may blur the effect of ICD on delay discounting (Joutsa et al., 2015). In the absence of further evidence, we can only conclude that higher delay discounting might indicate higher likelihood of ICD but the actual emergence of ICD likely depends on many other interacting factors.

Interestingly, a similar heterogeneity of results was observed regarding the relationship between response inhibition and ICD. Studies which investigated response inhibition in ICD obtained mixed findings, showing either impaired or spared stopping mechanisms (Palermo and Morese, 2018). Thus, typical delay discounting measures (using monetary rewards) may capture the same phenomenon of inhibition deficit as response inhibition tasks do in patients with ICD. Delay discounting tasks using rewards adapted to patients' specific behavioral addictions might be more sensitive to increased reward wanting (than to impaired inhibition) and thus make altered discounting more clearly salient in ICD.

Aside from purely behavioral aspects, neuroimaging results suggest that ICD in PD patients is associated with modified neural mechanisms underlying future-oriented decision-making during the delay discounting task (see main regions involved in Fig. 3B). A study which investigated fMRI activation during a delay discounting task (with erotic images) in PD patients with hypersexuality disorder evidenced an altered functioning of ventral medial prefrontal cortex (vmPFC), a core region of valuation system, in PD patients with hypersexuality disorder while evaluating the option to wait to view erotic images for longer (Girard et al., 2019). Activity in the vmPFC was positively correlated with delay duration in these patients (in contrast with non-impulsive PD

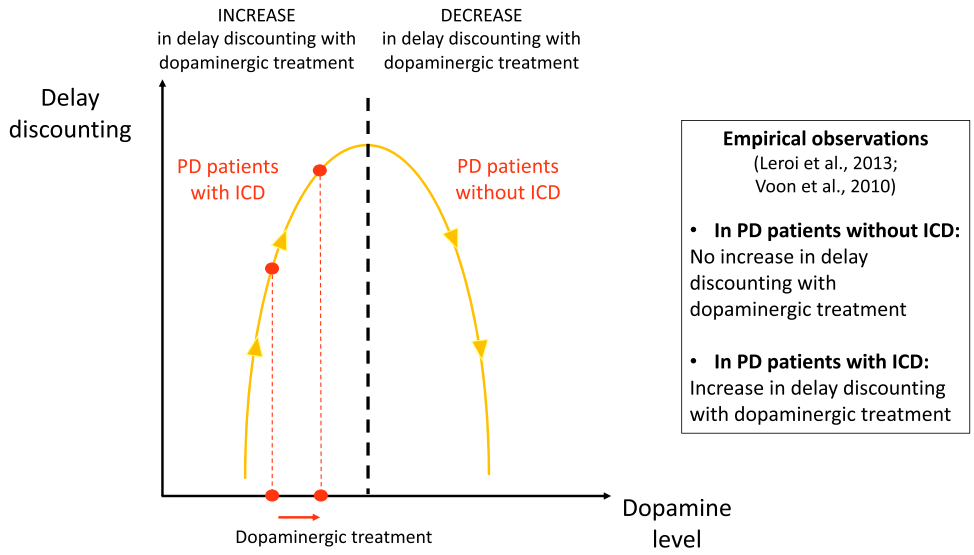

Fig. 4. Theoretical inverted U-shape relationship between dopamine and delay discounting. This theory is consistent with observations regarding the impact of dopaminergic treatment in Parkinson's disease with and without impulse control disorder (ICD)). PD patients with ICD might be characterized by increased delay discounting after dopamine administration.

patients and controls), which probably indicated that their valuation system no longer coded increasing delays as a cost but rather as a mean to obtain erotic rewards for longer (Girard et al., 2019). Besides, another study found that while choosing between the immediate and delayed reward options, PD patients with ICD showed a decreased activation in the right dorsal striatum (compared to both non-impulsive PD patients and healthy controls) (Filip et al., 2018). An increased connectivity from striatum to the salience-associated left insula and to bilateral calcarine cortices was also observed in PD patients with ICD, suggesting that ICD neurological mechanisms are not limited to the dopaminergic reward system (Filip et al., 2018).

3.4. Links between delay discounting and treatments of PD

3.4.1. Impact of dopamine replacement therapy on delay discounting

Antiparkinsonian dopamine replacement therapy (DRT) often include dopamine agonists (compounds that activate dopamine receptors) and/or levodopa (an amino acid precursor of dopamine). DRT allows to directly investigate the causal role of dopamine on intertemporal decisions by comparing regularly medicated PD patients in high ("on" medication) and low ("off" medication) dopaminergic states (e.g., two morning testing sessions, once while taking the usual medications and once after an overnight washout of the DRT). DRT has been associated to the emergence of ICD in patients with PD (Weintraub et al., 2006) but the exact role of delay discounting in this association is still unclear.

Results do not support the hypothesis of a systematic increase in delay discounting with increased dopamine level. Several studies (Foerde et al., 2016; Milenkova et al., 2011; Simioni et al., 2012) found that compared with patients "off" medication and healthy controls, PD patients "on" medication presented lower or similar discounting rates. Only one study (Antonelli et al., 2014) observed that PD patients "on" medication showed an enhanced activation of the medial prefrontal cortex and made more impulsive choices than "off" for high reward magnitudes.

There might be an interaction effect between dopamine status and ICD status, explaining the absence of systematic increase in delay discounting in the "on" medication status. According to two studies (Leroi et al., 2013; Voon et al., 2010), dopamine administration would be associated with greater discounting of delayed rewards only in PD patients with ICD. Thus, ICD onset may correspond to a maladaptive response to non-physiological chronic dopaminergic treatment.

3.4.2. Impact of brain stimulation on delay discounting

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective and widely used treatment for motor symptoms in PD. Subthalamic Nucleus Deep Brain Stimulation (STN-DBS) is supposed to have neurorestorative effects in the nigrostriatal and mesolimbic dopaminergic systems (Fauser et al., 2021). This treatment may therefore have an impact on delay discounting, like DRT. Converging evidence indicate changes in patients' decision-making behavior with STN-DBS, impulsivity and ICD being the most commonly documented manifestations (see (Broen et al., 2011) for a review), but the role of delay discounting in this effect is unknown.

Results suggest that STN stimulation is not directly related to the delay discounting facet of impulsivity. A total of four studies (Aiello et al., 2019; Evens et al., 2015; Seinstra et al., 2016; Seymour et al., 2016) could not evidence any major effect of STN-DBS on delay discounting either by comparing patient subgroups with and without STN-DBS or by testing the effect of acute STN-DBS (using a postoperative stimulation -on/ -off design). According to Aiello and coll. (Aiello et al., 2019), even PD patients who after DBS experienced weight gain and/or eating alterations did not present an increased temporal discounting for food rewards. A first reason which could explain the lack of evidenced impact of STN-DBS on delay discounting is that different variables influence this impact and blur the results. In particular, the effects of STN-DBS may interact with the effects of DRT and with the ICD status of PD patients (like the effects of DRT). The interaction with ICD status should be further investigated by future studies exploring the effects of STN-DBS. Another reason worth considering to justify these null findings is the absence of a link between the STN activity and delay discounting. Over the last 20 years, anatomical and behavioral data especially in animal models have suggested that the STN should play a critical role in frontal functions such as attention, inhibitory control, and motivation (Baunez and Lardeux, 2011). Moreover, impairments of the STN as well as other core dopaminergic areas such as ventral tegmental

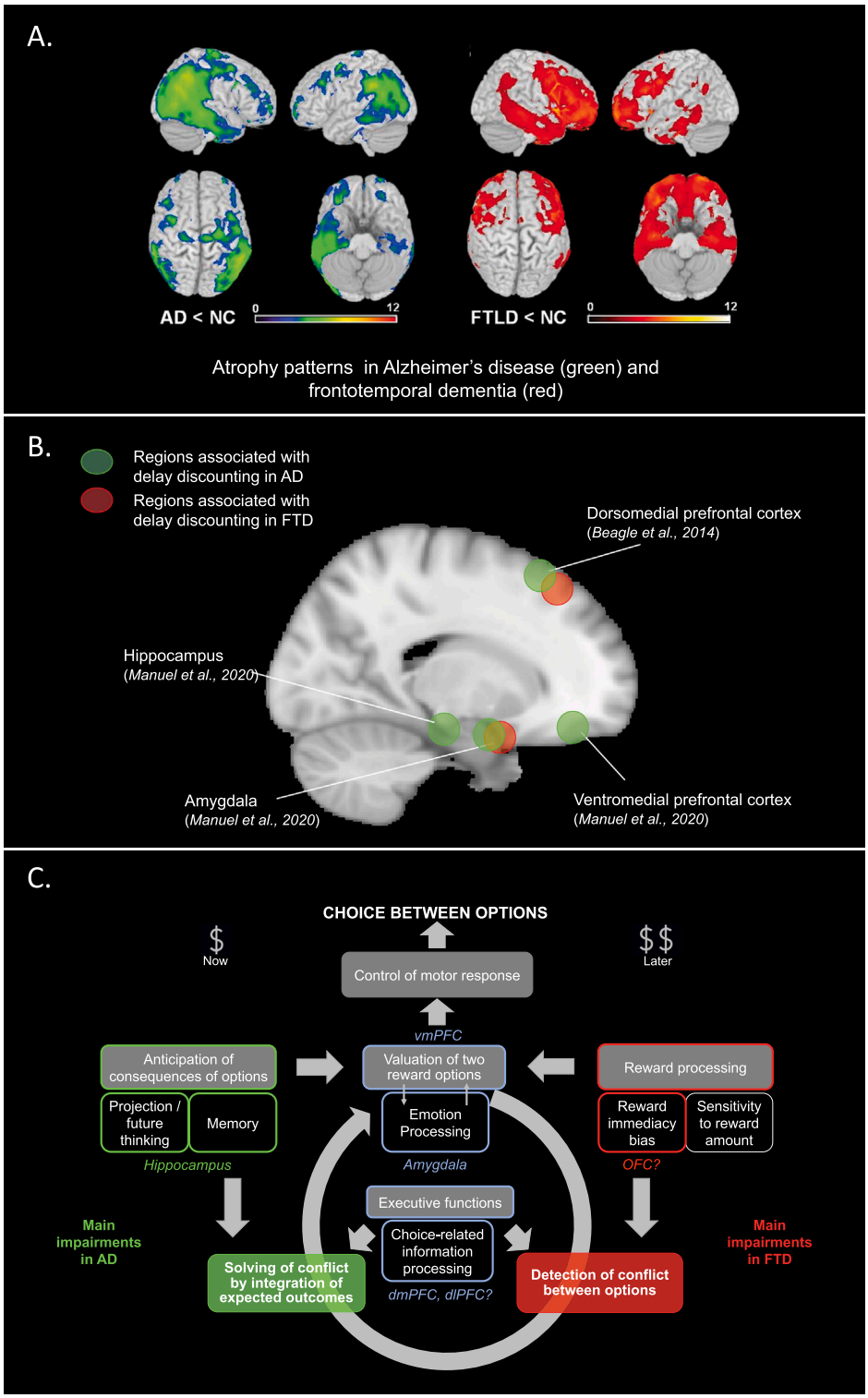

Fig. 5. Neuropathology and mechanisms of delay discounting in Alzheimer's disease (AD) and frontotemporal dementia spectrum (FTD). (A) Atrophy distribution obtained from the earliest MRI scans of autopsy-proven AD (left) and FTD (right) (results from (Rabinovici et al., 2008)); (B) Brain regions related to delay discounting in studies involving patients with AD and FTD; (C) Neurocognitive model explaining altered delay discounting in AD and FTD. Mechanisms evidenced to be disturbed in AD, FTD and in both conditions are circled in green, red and blue respectively. Brain regions shown or assumed (?) to be involved in altered discounting in AD, FTD and in both conditions are in green, red and blue respectively.

area and substantia nigra are known to be involved in conditions characterized by altered discounting such as externalizing disorders (Frost and McNaughton, 2017). However, one can notice that these regions have rarely been empirically related to delay discounting in healthy populations (see Frost and McNaughton, 2017 for a review of empirical findings) and the main neurobiological models of delay discounting do not include them (Lempert et al., 2019; Peters and Büchel, 2011).

Another brain stimulation technique which has been more investigated over the past decade is transcranial direct current stimulation (tDCS). tDCS is a neuromodulatory technique based on the application of weak, direct current over the scalp, leading to cortical hypo- or hyperpolarization according to the specified parameters. A recent study assessed the effect of anodal tDCS over the dorsolateral PFC on reward responsiveness and delay discounting in PD patients with ICD. Of note, tDCS was not found to modulate the altered wanting and discounting of rewards observed in PD patients with ICD (Terenzi et al., 2021).

3.5. Theoretical and clinical implications

3.5.1. Neurocognitive model of altered delay discounting in PD

Although there is not much empirical evidence of the direct links between neurocognitive measures and altered discounting in PD, we can make assumptions based on the clinical features of PD. In a previous section, we have detailed the possible involvement of reward processing, emotional processing, and executive dysfunction in altered discounting. Troubles to process external information have been identified specifically in PD patients with ICD, who behaved as if they could not use the information provided within the experimental context to obtain future rewards (Averbeck et al., 2013). Higher sensitivity to reward amount has also been detected in PD patients with ICD (Girard et al., 2019).

Within the framework of our neurocognitive model of delay discounting, we assume that PD patients, like bvFTD patients (see Section 3.4.1), present a high reward immediacy bias and high difficulties to detect conflict between options (see Fig. 3. C), which prevents the iterative adjustment of option valuation. This assumption is in accordance with a study which showed, through factor analysis of different measures of impulsivity in PD, that delay discounting loaded on a factor conceptually corresponding to a general preference for immediacy of outcome (Nombela et al., 2014).

3.5.2. A U-shaped relationship between dopamine and delay discounting

Observed effects of the manipulation of dopamine in PD patients support the theory of an inverted U-shaped relationship between delay discounting and the dopaminergic system. As detailed in Fig. 4, the administration of dopamine may increase or decrease temporal discounting, depending on how the administration shifts temporal discounting on the U-shaped curve (which depends on the baseline dopamine level and administered dose) (Joutsa et al., 2015). Consistent with this assumption, Joutsa et al. (Joutsa et al., 2015) observed population-dependent effects of dopamine agonists using positron emission tomography (PET). In PD patients, an increased dorsal striatal dopaminergic function was associated with higher discounting while in the whole sample of pathological gamblers and controls, an increase in ventral striatal dopaminergic function was related to lower discounting. The theory of an inverted U-shaped relationship between delay discounting and dopamine (Joutsa et al., 2015) could also explain the heterogeneous impacts of DRT observed in PD patients and the observed interaction between the effect of dopamine and ICD status (Leroi et al., 2013; Voon et al., 2010). Relying on this theory, it is possible that PD patients developing ICD present lower baseline dopamine level even under regular DRT treatment and thus shift on the increasing side of the inverted U after dopamine administration (in the “on” medication status). In contrast, patients with no ICD may have a sufficiently high baseline dopamine level with regular DRT so that they shift on the decreasing part of the U when “on” medication (see Fig. 4). This would explain why dopamine administration is associated with greater discounting of delayed rewards only in PD patients with ICD (Leroi et al., 2013; Voon et al., 2010).

3.5.3. Using the delay discounting task as a clinical tool to prevent ICD

The intertemporal choice task could become very helpful to predict and avoid the risk of ICD emergence in PD as a maladaptive response to DRT. In a previous section, we described mixed findings in the literature regarding the level of discounting in PD patients with ICD compared to PD patients without ICD. However, the results of two studies (Leroi et al., 2013; Voon et al., 2010) suggest that an increase in delay discounting with dopamine administration may be more characteristic of PD patients with ICD (compared to patients without ICD) than a higher absolute level of discounting (see Fig. 4). Therefore, assessing the evolution of delay discounting before and after the first DRT administration may contribute to predict ICD emergence. Moreover, the most adapted dose of dopaminergic treatment avoiding ICD might be detected when acute dopamine agonist administration stops resulting in an increase in delay discounting. This possibility should be further investigated by longitudinal studies and more generally, future studies of delay discounting in PD should account for individual differences in baseline dopamine to fully understand the complex effects of dopamine on choice impulsivity.

4. Delay discounting in alzheimer disease and frontotemporal dementia

After describing the main characteristics of AD and FTD conditions, this section summarizes observations of studies investigating discounting modifications across the AD and FTD spectrum. We detail evidence that discounting is altered in both AD and FTD and we provide arguments supporting the role of four neurocognitive processes in the alteration of discounting in these conditions. The section ends with the description of implications regarding: 1. the theoretical modeling of mechanisms underlying modified intertemporal preferences in AD and FTD; 2. the clinical value of the delay discounting task for the differential diagnosis of AD and the behavioral variant of FTD.

4.1. Clinical-neuropathological hallmarks of AD/FTD

AD and FTD can sometimes be difficult to differentiate but typical clinical symptoms allow to distinguish them: amnestic AD begins with episodic memory loss while FTD, in contrast, describes a group of clinical syndromes in which behavioral or language symptoms predominate (Mendez et al., 1996). AD and FTD also present different patterns of atrophy, assumed to correspond to distinct large-scale networks (Zhou and Seeley, 2014). Fig. 5A. shows the characteristics of atrophy patterns in AD and FTD.

4.1.1. Clinical-neuropathological hallmarks of AD spectrum

Today much attention is paid to the preclinical and prodromal stages of dementia, particularly Alzheimer’s dementia (AD). Since the 1990 s, the early clinical phase in AD has been designated by the term Mild Cognitive Impairment (MCI) (Petersen, 2004; Petersen et al., 1999; Winblad et al., 2004). The introduction of the concept of MCI emphasized that cognitive decline in AD is progressive: mild deficits are present before the onset of a dementia syndrome. Today, the term "prodromal AD" translates into modern terms what was once designated as "MCI due to AD". In recent years, it has become clear that MCI is not specific to AD, even though AD is the most common cause. In the present work, we use the MCI label because it is the one which is used in the studies examined for our purpose. Neuropsychological evaluations reveal that patients with MCI present an impairment in one or more cognitive domain (typically including memory), below expectations for their age and education. However, in opposition to patients with AD dementia, patients with MCI are still able to perform normal daily activities and to make some appropriate choices in their everyday life (Feinberg and Whitlatch, 2001).

Clinically, AD dementia stage is defined by an impairment in at least two cognitive domains which interferes with the ability to function in daily living (which is the main condition for a diagnosis of dementia) (McKhann et al., 2011). In this review, AD refers to the most common syndromic presentation of AD dementia, the amnestic presentation. It is characterized by an impairment in learning and recall of recently learned information as well as in at least one other cognitive domain (reasoning and handling of complex tasks and poor judgement; visuospatial abilities; language functions; personality, behavior or comportment) (McKhann et al., 2011). Therefore, poor judgement, which includes decision-making ability, is among the diagnostic criteria for AD. The typical pattern of atrophy in the amnestic presentation of AD dementia includes the medial, basal, lateral temporal lobe, and medial and lateral parietal cortex (see Fig. 5A).

Table 2
Studies assessing delay discounting in patients with dementia and their main results[a].

Reference	Populations					Comparisons on delay discounting rate
	MCI	AD	bvFTD	svPPA	HC	
Beagle et al. (2020)		N = 15	N = 18	N = 17	N = 72	svPPA > bvFTD > AD = HC Sensitivity to choice attributes: AD < HC
Bertoux et al. (2015)		N = 30	N = 20		N = 20	bvFTD > AD = HC
Chiong et al. (2016)		N = 25	N = 28	N = 14	N = 61	svPPA > bvFTD = AD = HC
Coelho et al. (2017)	N = 55				N = 57	MCI = HC
El Haj et al. (2020)		N = 37			N = 40	AD > HC
El Haj et al. (2020)		N = 40			N = 42	AD > HC
Forstmeier et al. (2015)	N = 64	N = 47				MCI = AD at baseline Increase only in AD after one year
Geng et al. (2020)	N = 22	N = 37			N = 51	AD > HC and MCI > HC for intermediate and large relative differences between SS and LL
Lebreton et al. (2013)		N = 20	N = 14		N = 20	AD and bvFTD > HC; AD > HC especially when delayed reward has to be mentally imagined
Lempert et al. (2020)	N = 74				N = 26	MCI > HC
Lindbergh et al. (2014)	N = 25				N = 39	MCI > HC especially for small reward magnitudes
Manuel et al. (2020)		N = 15	N = 22		N = 15	bvFTD > AD and HC AD > HC with negative emotion priming
Mariano et al. (2020)		N = 25	N = 27		N = 24	bvFTD = AD = HC Magnitude effect: bvFTD and AD < HC
Thoma et al. (2017)	N = 64	N = 47				Stable in MCI over 2 years Increase in AD over 2 years

[a] Only the main results regarding comparisons on behavioral measures of delay discounting (or other outputs like sensitivity to trial attributes) are described here. MCI: mild cognitive impairment; AD: Alzheimer's disease; bvFTD: behavioral variant frontotemporal dementia; svPPA: semantic variant primary progressive aphasia; HC: healthy controls; SS: smaller sooner option of reward; LL: larger later option of reward.

4.1.2. Clinical-neuropathological hallmarks of FTD spectrum

There are other forms of primary degenerative dementias, less frequent than AD, such as frontotemporal dementia (FTD). FTD is the most common of a group of clinical syndromes associated with predominant degeneration of the prefrontal and temporal regions and non-Alzheimer type pathology, which has been called frontotemporal lobe degeneration (FTLD) (Neary et al., 2005). Distinct clinical syndromes constitute the FTD spectrum and include the behavioral variant (bvFTD) as well as primary progressive aphasias such as the semantic variant primary progressive aphasia (svPPA, previously known as semantic dementia) (Chare et al., 2014; Karageorgiou and Miller, 2014). BvFTD, the most common clinical variant, is characterized by significant changes in personality and behavior. The main clinical symptoms observed in bvFTD patients are behavioral disinhibition (in particular socially inappropriate and risky behaviors), apathy, loss of empathy, early perseverative, stereotyped or compulsive/ritualistic behavior and hyperorality and dietary changes (Rascovsky et al., 2011). In svPPA, the most prominent clinical feature is language deficits, including impaired ability to retrieve words and impaired single-word comprehension, but it may also cause changes in personality and behavior like in bvFTD (Gorno-Tempini et al., 2011). In all FTD syndromes, and in contrast to AD, memory and visuospatial abilities are relatively spared at the beginning of the disease. BvFTD and svPPA variants present overlapping but distinct anatomical substrates. While the bvFTD variant is associated with greater brain damage in frontal and insular regions than in the temporal regions, svPPA is associated with greater damage in anterior temporal regions than in frontal and insular regions (Chare et al., 2014; Karageorgiou and Miller, 2014). Brain regions known to be related to reward and emotion processing such as the orbitofrontal cortex (OFC), ventromedial prefrontal cortex (vmPFC) and ventral striatum (Bartra et al., 2013; Levy and Glimcher, 2012; Rangel and Clithero, 2012) are often affected in both these forms of FTD (Chare et al., 2014; Karageorgiou and Miller, 2014) (see Fig. 5A).

4.1.3. Potential links with delay discounting

Both AD and FTD present symptoms and atrophy patterns which suggest a possible alteration of delay discounting. In particular, the impairment of executive functioning often observed in both AD (Patterson et al., 1996) and FTD (Rascovsky et al., 2011) suggests that delay discounting should be steeper in both conditions compared to controls. Overlapping but also distinct mechanisms are probably involved in the modified delay discounting in the two conditions.

In the AD spectrum, atrophy of medial temporal areas may contribute to symptoms of decision-making deficits and in particular to altered delay discounting. There is converging evidence of decision-making deficits in both MCI (Han et al., 2015; Triebel et al., 2009) and AD patients, in particular for medical decisions (for example, decisions about beginning, continuing, or terminating medical treatment) (see (van Duinkerken et al., 2018) for a review). Besides, memory-related medial temporal areas have been shown to contribute to individual differences in delay discounting in healthy populations (Benoit et al., 2011; Lebreton et al., 2013; Lempert et al., 2020a; Peters and Büchel, 2011).

In FTD, altered delay discounting may manifest through impulsive symptoms closely associated with neurodegeneration in the orbitofrontal cortex (OFC). Damages in the OFC have been related to inhibition deficits in FTD (Godefroy et al., 2021; Tanguy et al., 2022) and across neurodegenerative conditions (Migliaccio et al., 2020) and in general, patients with damage to the OFC tend to make impulsive decisions about relationships or money, without considering the long-term consequences of their actions (Gleichgerrcht et al., 2010). Moreover, the OFC has been very often associated to individual differences in delay discounting (e.g., (Bartra et al., 2013; Cooper et al., 2013; Peters and Büchel, 2011)).

All delay discounting studies in AD and/or FTD reviewed in this work to explore these hypotheses are summarized in Table 2, along with their main behavioral results. These studies evidenced specific brain regions related to delay discounting in AD and/or FTD, as shown in Fig. 5B.

4.2. Modifications of delay discounting across the AD and FTD spectrum

4.2.1. Altered delay discounting across the AD spectrum

In MCI, changes in delay discounting have been sparsely studied. Only four cross-sectional studies have investigated delay discounting in patients with well-defined criteria for MCI compared with matched healthy controls (Coelho et al., 2017; Geng et al., 2020; Lempert et al., 2020b; Lindbergh et al., 2014b). Together, the results of these studies suggest that MCI patients show increased discounting rates, especially for small amounts of delayed reward but with high relative differences between the most immediate and the delayed reward.

Though there is more work investigating delay discounting in AD patients, findings are more mixed. Five studies (El Haj et al., 2020b,

2020a; Geng et al., 2020; Lebreton et al., 2013; Manuel et al., 2020) confirmed that AD participants showed higher delay discounting than matched healthy controls, in particular for high relative differences between the immediate and delayed reward like in MCI patients (Geng et al., 2020). On the opposite, in four other studies (Beagle et al., 2020; Bertoux et al., 2015a; Chiong et al., 2016; Mariano et al., 2020), patients with AD had similar intertemporal preferences to those observed in healthy controls. There was no obvious difference in the severity of AD disease between these two groups of studies. Thus, discrepancies might be due to other methodological differences such as the sample size (studies which found significant effects had higher sample size in the AD group compared to studies which did not) or the specificities of the delay discounting paradigm (e.g., negative emotion priming in Manuel et al., 2020).

Comparisons between MCI and AD patients on delay discounting suggest that the transition from MCI to AD may be manifested in subtle changes, in particular in the trajectory of evolution of delay discounting. Two longitudinal studies (Forstmeier and Maercker, 2015; Thoma et al., 2017) showed distinct trajectories over a time interval of one or two years: AD patients showed an increase in delay discounting while MCI maintained stable performance. The transition from MCI to AD may also be manifested by progressive changes in the so-called "magnitude effect" generally observed in non-cognitively impaired individuals (Kirby and Maraković, 1996), that is the tendency to discount small rewards more than large rewards. On the 2-year interval of the longitudinal study by Thoma and colleagues, this typical "magnitude effect" persisted only in the MCI and disappeared in the mild AD patients. This was confirmed by another study (Mariano et al., 2020) which showed that AD patients were less sensitive to magnitude effects compared to controls.

4.2.2. Altered delay discounting in the FTD spectrum

Most studies (five out of six) which investigated delay discounting in FTD found higher delay discounting in FTD patients compared to controls (Beagle et al., 2020; Bertoux et al., 2015a; Chiong et al., 2016; Lebreton et al., 2013; Manuel et al., 2020). The only study which did not confirm this result suggested another modification in bvFTD compared to controls: a lower magnitude effect (i.e., lower tendency to discount small rewards more than large rewards) (Mariano et al., 2020). Results of the two studies which compared svPPA and bvFTD suggest that bvFTD patients discount future rewards to a lesser extent than svPPA patients (Beagle et al., 2020; Chiong et al., 2016).

Although most studies comparing AD and FTD observed higher discounting in FTD (Beagle et al., 2020; Bertoux et al., 2015a; Manuel et al., 2020), typical monetary paradigms failed to consistently differentiate bvFTD from AD patients. In particular, Mariano and colleagues could not find evidence for any difference between bvFTD and AD on the delay discounting task in spite of the observed discrepancy between the two groups on a measure of impulsivity based on caregiver's report (bvFTD showing higher impulsivity) (Mariano et al., 2020). As detailed in the next subsection, other paradigms might be more sensitive to distinguish bvFTD and AD, as they emphasize mechanisms that are differentially involved in delay discounting in the two conditions.

4.3. Four mechanisms involved in altered delay discounting in AD and FTD

In view of their different brain atrophy patterns and associated clinical symptoms, it is very likely that delay discounting is altered for distinct, although partially overlapping, reasons in AD and FTD. In the next subsections, we present evidence from studies in AD and FTD supporting that at least four different mechanisms would contribute to alter delay discounting in these conditions. We show that in both AD and FTD, impairments of emotional processing and choice-related information processing may contribute to modify delay discounting. Moreover, heightened reward immediacy bias would explain altered discounting mostly in FTD while impairments of projection in the past/future would impact discounting especially in AD.

4.3.1. Emotional processing

AD and FTD feature opposing symptom profiles in terms of emotional processing, which may relate to their patterns of atrophy targeting distinct large-scale networks. Thus, emotions may modulate delay discounting differently in these two conditions. While AD patients present intensified emotions (which may take the form of anxiety or other affective symptoms) and preserved emotional connectedness, patients with bvFTD and right svPPA become progressively cold, detached, and tactless, and fail to show emotional empathy (Zhou and Seeley, 2014).

Damage to a number of brain structures within the temporal and frontal lobes, including inferior temporal regions, amygdala, orbitofrontal cortex and insula, have been implicated in the impairment of emotion processing observed in FTD. Damage to these brain regions may interfere with a number of processes underlying the evaluation, regulation and expression of emotional information (Kumfor and Piguet, 2012). FTD (bvFTD in particular) and AD show opposing large-scale network changes which contribute to predict their divergent patterns of emotional symptoms. BvFTD targets a large-scale network referred to as the "salience network" (SN - anchored in the anterior insula and dorsal anterior cingulate cortex) which activates in response to emotionally significant ambient stimuli and events (Seeley, 2019). Alzheimer disease, in contrast to bvFTD, targets a large-scale network often referred to as the "default mode network" (DMN - including posterior cingulate-precuneus, medial temporal, lateral temporoparietal, and dorsomedial prefrontal regions) which deactivates during cognitively demanding tasks (Greicius et al., 2003; Raichle, 2015). Data suggest that progressive damage to either network (SN or DMN) intensifies activity and connectivity in the other network, perhaps due to disrupted inhibitory interactions between the two networks (Seeley et al., 2012). Therefore the SN, in charge of emotional response, is disrupted in bvFTD but enhanced in AD, which may explain the opposite emotional profiles in AD (emotional intensification) and bvFTD (emotional blunting).

A delay discounting paradigm using emotional priming allowed to show that patterns of modulation of discounting by emotions were modified differently in bvFTD and AD as compared to controls (Manuel et al., 2020). In this version of the task, prior to each choice, an emotional picture (either positive, negative or neutral) was presented for five seconds and participants were instructed to vividly imagine that they were witnessing the event/content depicted in it. BvFTD patients had increased delay discounting compared to AD and controls, and contrary to controls, they did not show any modulation according to emotional priming. In contrast, AD patients showed increased discounting compared to controls exclusively when primed by negative emotions. Aside from the impairment of emotional processing, cognitive issues impacting mentalizing and anticipatory abilities in AD and FTD may also prevent the expected emotional enhancement with emotional pictures. However, results of this study suggested: on the one hand, an intensification of negative emotions in AD causing an increase in discounting; on the other hand, an emotional blunting in FTD resulting in a lack of modulation of discounting by emotional picture, which is consistent with expectations from their respective emotional clinical profiles.

Further analyses of structural MRI in the same study highlighted the central role of grey matter integrity in bilateral amygdala in the modulation of delay discounting by negative emotions (Manuel et al., 2020). Group-specific analyses revealed that this association was mediated primarily by the AD group. In AD patients, increased delay discounting in the negative emotion condition was also correlated with reduced grey matter integrity in ventromedial prefrontal cortex (vmPFC), and in parahippocampal gyri. This last result suggests that there is an interaction between impaired emotion-related, memory-related and valuation-related brain regions which determines the modifications of intertemporal preferences in AD patients.

4.3.2. Integration of trial information

Exploration of delay discounting mechanisms in AD and FTD suggests a failure to integrate quantitative information in value-based decision-making in both conditions. Beyond the estimation of impulsivity, the study by Beagle and colleagues estimated subject-level sensitivities to three attributes of choice (the relative difference in reward magnitude, delay length, and delayed reward magnitudes) in AD, bvFTD and svPPA patients. Although patients with AD did not differ from controls in their global delay discounting tendency, the decisions of AD patients were less influenced by the three attributes of choice (Beagle et al., 2020). BvFTD and svPPA patients showed higher discounting than controls and also presented an attenuated sensitivity to trial attributes, but to a lesser extent than in AD.

The analysis of brain structural correlates of sensitivity to trial attributes in Beagle's study suggests a key role of the dorsomedial prefrontal cortex in integrating quantitative attributes of choice in value-based decision-making. The association between attenuated sensitivity to information and dorsomedial prefrontal atrophy was observed across AD and FTD but was driven in particular by the AD group. Dorsomedial prefrontal cortex is indeed known to play a key role in the context of complex decision-making, with lots of information to integrate (Venkatraman et al., 2009).

4.3.3. Reward immediacy bias

Impaired reward processing and in particular enhanced reward immediacy bias are likely to be the central mechanisms underlying higher discounting in the FTD spectrum. Indeed, a form of urgency may systematically drive FTD patients towards the choice of the immediate reward options, regardless of other possible options in the future.

Several arguments from the neuropathology and symptomatology of FTD support increased reward immediacy bias in this condition. First, FTD patients show high impulsivity related to atrophy of orbitofrontal cortex (OFC); a potential link between the OFC reward-related function and impulsive behavior is that impulsive people show a higher tendency to approach reward and a lower tendency to escape punishment (Berlin, 2004). Besides, changes in dietary and eating behavior are common manifestations of FTD, in particular altered food preferences with carbohydrate cravings and binge eating. These symptoms also suggest steeper reward immediacy bias (in particular with food) in FTD.

There is no direct evidence that heightened reward immediacy bias is involved in the alteration of delay discounting in FTD. However, results suggest that with some specific rewards that are easy for patients to imagine and understand (especially primary rewards represented by food items), bvFTD patients are very likely to systematically choose the smaller immediate rewards than the larger delayed reward (Bertoux et al., 2015a). Moreover, no correlation was observed between delay discounting and cognitive scores assessing memory, executive function, language or social-cognition, suggesting that these cognitive functions are not involved in the modifications of intertemporal preferences in bvFTD (Bertoux et al., 2015a).

4.3.4. Projection in the past and future

Observations in AD patients suggest that deficits in autobiographical memory and future thinking are highly involved in modified delay discounting (El Haj et al., 2020b, 2020a). It is likely that decline in future thinking in AD, like decline in autobiographical memory, would limit the ability of patients to evaluate the outcomes of their decisions over time. A first study (El Haj et al., 2020a) in mild AD patients observed significant negative correlations between delay discounting and autobiographical memory. Importantly, correlations between delay discounting and autobiographical memory remained significant even after controlling for general cognitive function. The second study by El Haj and coll. (El Haj et al., 2020b) found that higher delay discounting was associated with lower future thinking in AD.

In the same vein, a study compared impulsive choices in AD and bvFTD for trials in which the delayed option had to be mentally simulated and trials in which the delayed option could be visually observed (Lebreton et al., 2013). Pathological impulsivity was specifically revealed in the condition requiring mental simulation in AD patients, while it was exhibited irrespective of the condition in bvFTD patients. This last result confirmed that the involvement of mentalization and future thinking troubles in the alteration of discounting was specific to AD.

Like AD patients, svPPA patients have deficits in projecting themselves into the future, probably related to their higher atrophy in temporal regions (Duval et al., 2012; Irish et al., 2012a, 2012b). This projection deficit observed in svPPA but not in bvFTD may explain why svPPA patients discount future rewards to an even greater extent than bvFTD patients. This specific impairment may indeed add up to the heightened reward immediacy bias shared with bvFTD.

4.4. Theoretical and clinical implications

4.4.1. Neurocognitive model of altered delay discounting in AD and FTD

Relying on the presented literature on delay discounting in AD and FTD and on knowledge of their respective neuropathology, one can assume that impairments of emotional processing, information processing and executive functions contribute to altered delay discounting in both conditions. Moreover, heightened reward immediacy bias could primarily explain altered discounting in FTD, while impairments of projection in the past/future may explain altered discounting in AD.

Within the framework of our neurocognitive model (see Fig. 5.C.), we assume that high reward immediacy bias in FTD would impair the capacity to detect conflict between the SS and LL options and would thus prevent the delayed process of iterative adjustment of option valuation. The impact of memory and future thinking deficits on delay discounting in AD would be more indirect: it would not prevent conflict detection (thus value update would remain possible) but it would alter the capacity for correct solving of the detected conflict by the integration of previous experiences. These predictions of the model are consistent with observations made by Bertoux et al. (Bertoux et al., 2015a) regarding the specificities of FTD and AD patients' behavior in the delay discounting task. Indeed, they noticed that FTD patients tended to systematically prefer the SS option (without any conflict) and globally showed more impulsive choices than AD patients. In contrast, AD patients showed higher preference for the SS option compared to controls only in cases of conflict between options that were difficult to solve (e.g., with long delay but high LL value or short delay but small LL value) (Bertoux et al., 2015a). In addition, other decision-making tasks such as the Iowa Gambling Task suggest that in AD, decision-making is not impulsive and 'risky' per se like in FTD, but can be problematic owing to randomness (Gleichgerrcht et al., 2010). Indeed, patients with AD tend to alternate frequently between safe and risky choices during the task, which may result from a difficulty to develop a stable advantageous strategy to solve detected conflicts between possible options.

4.4.2. Using the delay discounting task as a clinical tool for differential diagnosis

The delay discounting task might serve as a preclinical diagnostic instrument to detect MCI patients, at risk of developing AD, or as a tool predicting transition from MCI to AD. Some specific aspects of the task (like the magnitude effect) may evolve across stages of cognitive decline and thus contribute to make prognosis about the evolution of the disease.

It is more likely that the delay discounting task could provide further insight into the differential diagnosis of bvFTD and AD. Combinations of traditional neuropsychological tests can contribute to the differential diagnosis of FTD and AD (Diehl et al., 2005; Thompson, 2005). However, FTD is associated with a profound behavioral syndrome that affects performance on cognitive assessment, obscuring group differences. Numerical scores on neuropsychological tests alone are of limited value in differentiating FTD and AD (Thompson, 2005). Among FTD

conditions, the diagnosis of bvFTD remains particularly challenging and some patients may be misdiagnosed as suffering from AD (Rascovsky et al., 2011). In the absence of definitive biomarkers, the diagnosis of bvFTD is dependent on the identification of the syndrome's core symptoms associated with frontal lobe dysfunction. Disinhibition and general impulsivity are among the prominent symptoms of bvFTD (Godefroy et al., 2021; Paholpak et al., 2016; Rascovsky et al., 2011). A few tests are already available to objectively assess different facets of impulsivity in patients: the Stroop and Hayling tests to assess cognitive difficulties to inhibit prepotent responses as well as the Go/No-Go and Stop Signal tasks to assess motor inhibition deficits (Migliaccio et al., 2020). The delay discounting task could complement these tasks by evidencing other aspects of impulsivity, in particular decisional impulsivity. Moreover, by simulating choices between reward options, this task allows to target reward processing impairments, which are also key features of bvFTD. Tasks assessing reward processing are not commonly used in clinical practice but for the differential diagnosis of bvFTD, these types of tests using rewards as stimuli could be a great added value. In particular, the use of primary rewards belonging to the food domain may be optimal, as the increased reward immediacy bias specific to bvFTD condition is especially salient in this domain (Rascovsky et al., 2011). Further, modified versions of the delay discounting task (for instance contrasting trials in which the delayed option has to be imagined with trials in which the delayed option can be visualized) may also help to distinguish AD patients from bvFTD patients.

In addition, intertemporal choice performances could contribute to stratify patients into subgroups likely to be different in terms of genetic causes, distribution of brain damage and disease progression. For instance, using statistical classification approaches, behavioral measures of inhibition deficits as well as measures of apathy subtypes have shown their capacity to classify bvFTD patients into distinct anatomical subtypes (with distinct patterns of atrophy) (Godefroy et al., 2022, 2021). Conversely, the identification of subtypes of bvFTD based on distinctive patterns of atrophy (within specific functional networks targeted in bvFTD) has yielded interesting results in terms of genetic and neuropathological stratification (Ranasinghe et al., 2016). Indeed, this allowed to delineate a subset of bvFTD patients with primarily subcortical atrophy, who were more likely to have TDP-43 neuropathology and C9orf72 mutations. As delay discounting is a complex process potentially closely related to the functional networks specifically damaged in bvFTD (in particular the salience network), outcomes of this task may also contribute to stratify patients within the bvFTD spectrum.

5. Delay discounting from neurodevelopmental to neurodegenerative diseases: a continuum?

Results presented in the previous sections suggest that delay discounting is altered across neurodegenerative conditions (although with varying degrees) and it may also be a transdiagnostic marker of psychiatric conditions, including neurodevelopmental disorders (Amlung et al., 2019). A growing body of literature highlights relationships and overlap between neurodevelopmental conditions and neurodegenerative disorders (for reviews, see: (Magnin, 2021; Magnin et al., 2021; Ouellette and Lacoste, 2021; Schwamborn, 2018; Thibaut, 2022). Although mechanisms are still poorly understood, neurodevelopmental disorders and neurodegenerative conditions show similar genetic, molecular, neurobiological and clinical characteristics. Since delay discounting is a trait-like characteristic (Odum, 2011) with a significant level of genetic heritability (Anokhin et al., 2015, 2011), it might represent the expression of a common genetic background between some neurodevelopmental disorders and neurodegenerative conditions. As such, it would be a great candidate biomarker for the very early prediction of a risk of neurodegenerative process. We detail below a few examples illustrating a continuity between specific neurodevelopmental and neurodegenerative diseases but the links with delay discounting are only assumptions and would need to be investigated.

Attention deficit hyperactivity disorder (ADHD) has been associated with an increased risk of neurodegenerative diseases (Becker et al., 2021), in particular of Parkinson's disease (PD) (Baumeister, 2021; Fan et al., 2020). Patients with PD are 2.8 times more likely to have a preceding ADHD diagnosis than healthy controls (Fan et al., 2020). ADHD shares with PD some cognitive and neuropathological features: deficits in attentional and executive processes (Callahan et al., 2017) as well as dopaminergic dysregulations (Volkow et al., 2011). Moreover, children and adults with ADHD show steeper delay discounting (Beauchaine et al., 2017; Chen et al., 2021; Dias et al., 2013), which might constitute a marker of the impairments they have in common with PD patients.

Individuals with autism spectrum disorder (ASD) are also at higher risk of dementia, in particular early-onset dementia. Adults with ASD are approximately 2.6 times more likely to be diagnosed with dementia under the age of 65 compared to the general population (Vivanti et al., 2021). Specifically, a strong overlap between ASD and Alzheimer's disease (AD) has been observed, which could be explained by common genetic and biological mechanisms (Nadeem et al., 2021). In particular, intracellular accumulation of the amyloid beta protein (i.e., the main component of the amyloid plaques in AD pathology) and increased blood levels of its precursor have been detected in ASD (Bailey et al., 2008; Wegiel et al., 2012). Individuals with ASD also present altered delay discounting (Carlisi et al., 2017; Warnell et al., 2019), perhaps in association with an early amyloid pathology leading to AD in older age.

Finally, behavioral and neurobiological links have been demonstrated between schizophrenia and frontotemporal dementia (FTD). Very early onset FTD cases can be misdiagnosed as schizophrenia, due to the presentation of similar behavioral disturbances such as hyperphagia and disinhibition (Giamarelou et al., 2017; Gourzis et al., 2012). Brain structural characteristics were shown to be very similar between patients with schizophrenia and patients with behavioral variant FTD (bvFTD) (Koutsouleris et al., 2022). Moreover, schizophrenia shares substantial genetic similarities with FTD (Li et al., 2022) and has been linked to the C9orf72 variant, the most common genetic form of bvFTD (Koutsouleris et al., 2022). Increased delay discounting has been evidenced in schizophrenia (Ahn et al., 2011; Brown et al., 2018; Heerey et al., 2007; Linda et al., 2017; Weller et al., 2014); it might constitute a common underlying mechanism of the behavioral disorders shared with FTD.

Further longitudinal analyses should be done to explore the hypothesis of a continuity of altered delay discounting across the lifespan and to determine the exact role of this factor: is it only a marker of common features between neurodevelopmental and neurodegenerative diseases or does it play a causal role in the etiology of these diseases?

6. Conclusion

In this review, we focused on the following questions: 1. could the evolution of delay discounting across the lifespan be predictive of the neurodegenerative process? 2. how is delay discounting altered in Parkinson's disease, Alzheimer's disease, and frontotemporal dementia, and how do those alterations reflect specific aspects of the disease? We showed that delay discounting could provide a unifying structure for different behavioral and cognitive impairments observed across older age and neurodegenerative diseases. Elucidation of the specific neuropsychological processes related to altered delay discounting in different neurodegenerative conditions revealed shared mechanisms (e.g., deficits of valuation) and allowed us to highlight probable core mechanisms in each condition: dopaminergic-related reward processing issues in PD, memory and projection deficits in AD, increased reward immediacy bias in FTD.

Delay discounting evolves more as a function of increasing cognitive decline (in particular decision-making impairment) than as a function of increasing age. Although a few arguments suggest that delay discounting might be modified before the onset of symptoms of neurodegenerative diseases, it is still unknown whether altered discounting could

Box 2

Key outstanding questions for future research on delay discounting and neurodegeneration.

Is altered delay discounting an early predictor of neurodegeneration? How is the trajectory of evolution of delay discounting (from childhood to adulthood and from adulthood to older age) associated with the risk of neurodegeneration? Is the alteration of delay discounting with cognitive decline associated with brain pathophysiological changes?

Is altered delay discounting associated with genetic forms of neurodegenerative diseases? Is it a risk factor for neurological disorders across the lifespan, from neurodevelopmental to neurodegenerative diseases? Could it contribute to explain the possible continuity between these two types of diseases? Does it constitute the expression of a common genetic background between these two types of diseases?

Is altered delay discounting a transdiagnostic marker across neurodegenerative diseases or is it more specific to diseases with impulsivity troubles as major symptoms like PD and bvFTD?

What are the specific mechanisms involved in the alteration of delay discounting in each condition especially in early stages? More empirical studies are needed to dig further into the following questions:

- In PD: until which extent is the impaired reward processing contributing to alter discounting in PD without ICD and in PD with ICD? How does it interact with impaired emotion processing and impaired executive functions? Is the increase in discounting after dopamine administration really specific to PD with ICD? What are the links between alterations of dopaminergic system, cognitive mechanisms and discounting in PD?

- In AD: until which extent is the deficit of memory / projection contributing to alter discounting? How does it interact with impaired emotion processing and impaired executive functions? Do these impairments result in a specific difficulty to solve conflicts between alternatives?

- In FTD: until which extent is the high reward immediacy bias contributing to alter discounting? How does it interact with impaired emotion processing and impaired executive functions? Do these impairments result in a specific difficulty to detect conflict between options? Does the deficit of memory / projection in svPPA add up to other deficits of FTD, thus leading to more intense modification of discounting in svPPA than in bvFTD?

How to take advantage of the combined neurodegenerative models (overlap / contrast) to further disentangle the different cognitive mechanisms explaining delay discounting? And to figure out at which step of the global decision-making process each cognitive mechanism interferes?

Milestones towards translating delay discounting into clinical practice.

1. **Developing a standardized version of the task**: with a version adapted to the broad spectrum of neurodegenerative conditions (combining different types of rewards), identify the normative range in a large sample of controls, check again all the psychometric properties of the task (validity, reliability).
2. **Developing clinical scales to detect neurodegenerative diseases**: identify ranges of discounting across several neurodegenerative diseases at different stages (including pre-symptomatic), define cut-offs, and test accuracy (sensitivity-specificity) for classification (patient vs control) and also for prospective prediction of a risk of neurodegeneration in healthy population.
3. **Testing the potential of the task for more specific uses:**

– For the detection of ICD risk in PD: identify ranges of variations in discounting after dopamine administration in PD with / without ICD and in *de novo* PD, define cut-offs, and test accuracy for prospective prediction of risk of ICD;
– For the differential diagnosis of AD and FTD: optimize the task for this specific purpose (e.g., focus on food rewards), identify ranges of discounting in AD and FTD (early stages), define cut-offs, and test accuracy for classification (between AD and FTD). Accuracy for classification between subtypes (or profile identification) in AD and FTD could also be explored.

4. **Showing the added-value of the task**: for each potential clinical use, demonstrate the additional benefits of the delay discounting task compared to other neuropsychological tests.
5. **Facilitating clinical use**: create a user-friendly application with easy tools to compute delay discounting scores and get information of interest for clinical practice.

serve as an early marker of neuropathology. However, we can assume that assessing delay discounting could be an added-value to the early detection of neurodegeneration thanks to its sensitivity to changes in several cognitive domains such as executive functions, valuation and reward processing. The longitudinal evolution of delay discounting in the course of the neuropathological process should be further investigated.

We proposed a neurocognitive model involving different cognitive functions (valuation, emotion processing, reward processing, memory/ projection and executive functions) to explain the final choice between the immediate and delayed options. This model assumes that the valuation process can be optimized by iterative loops involving the detection of a conflict between options and the consecutive resolution of detected conflict. We suggest the common involvement of damaged valuation, emotion processing and executive functions (including choice-related information processing) in the alteration of discounting across PD, AD and FTD. However, the core mechanism underlying altered discounting may vary and delay discounting measures may reveal distinct impairments according to the specificities of each condition. In PD condition, we assume that altered delay discounting is mainly due to impaired reward processing which prevents conflict detection and optimized valuation. Results in PD tend to confirm the causal role of dopaminergic reward system in delay discounting, with the hypothesis of a U-shaped relationship between dopamine and discounting. The relationship between alterations of dopaminergic system, cognitive mechanisms and discounting remains to be clarified. For instance, dopamine has been shown to impact time perception (Fung et al., 2021; Mitchell et al., 2018), a critical component of value-based decision-making; this could be explored as another potential underlying mechanism of its effect on delay discounting. The role of the dopaminergic system in delay discounting could also be investigated transnosologically, across PD, AD and FTD. In FTD like in PD, the optimization of valuation would be

highly compromised due to increased reward immediacy bias and impaired detection of conflict between options. In AD, deficits of memory / projection would only impact the resolution of detected conflicts but would not prevent the whole process of valuation optimization. These predictions are consistent with empirical findings suggesting higher impatience in FTD than in AD.

The study of delay discounting in PD, AD and FTD also revealed potential interesting clinical applications. In PD, investigating the effects of dopaminergic treatments was informative especially regarding ICD symptoms. ICD seems to correspond to a maladaptive response to dopaminergic treatments, which is manifested in PD patients with ICD (contrary to patients without ICD) by an increased delay discounting in the "on" medication status compared to "off". These observations suggest that the delay discounting task could be used as a clinical tool to detect poor responding to dopaminergic treatment and thus predict ICD emergence in PD. In AD and FTD, the comparison of delay discounting indicated that this task could help for the differential diagnosis of AD and bvFTD, especially with adapted versions (e.g., using food stimuli). Although this has never been explored, the delay discounting task might also contribute to the differential diagnosis of parkinsonian syndromes, to distinguish PD from the various atypical parkinsonian disorders such as progressive supranuclear palsy, multiple system atrophy, and corticobasal syndrome (Mahlknecht et al., 2010). Aside from the discrimination between conditions, the task bears potential for the stratification within conditions, but this has never been investigated.

A few limitations in our methodology of systematic review need to be reported: 1. no pre-registration for the protocol of the present review was conducted; 2. we could not run any meta-analysis because we found a rather small number of studies addressing heterogenous questions; 3. results of studies on delay discounting in neurodegenerative diseases were extracted by only one author (VG) and risks of bias inherent to these studies were freely estimated by this same author. These limitations may have introduced bias in the reproducibility of the search process, as well as bias in the interpretation of results of the selected studies. However, our objective was broader than conducting a systematic review of empirical findings about delay discounting in neurodegeneration. With this work, it was also our intent to propose new theoretical ideas on: 1. the possible added-value of neurodegenerative models to investigate the involvement of specific brain systems in delay discounting; 2. the potential clinical applications of the delay discounting task in neurodegenerative diseases. For this purpose, we put effort into crossing the empirical findings in the strict domain of our review with broader knowledge of factors influencing delay discounting and with global expertise of neurodegenerative diseases and their clinical features.

Despite its potential for clinical use and theoretical advances in the field of decision-making, delay discounting is still largely underexplored in neurodegenerative diseases. There is a gap in the literature addressing delay discounting in less frequent neurodegenerative conditions, which should be addressed by future studies. Several characteristics of the studies included in this review may also lower the reproducibility of results and should be the object of more attention. Firstly, there is a great variability in the versions of the task used to assess delay discounting, and the impact of these variations does not seem to be fully understood yet. Moreover, delay discounting is impacted in a complex way by multiple covariables which are not always accounted for and effect sizes (or information allowing to calculate them) for between-group comparisons are often not reported. Samples of patients with neurodegenerative disease in which delay discounting is investigated are also problematic for several reasons: they are often too small, heterogenous, and not representative (since they are recruited in early stages of illness because of the cognitive demands of the task). Finally, the crossing of MRI data with delay discounting assessment is still rare in patients with neurodegenerative conditions (especially with dementia), which limits the understanding of the specific mechanisms underlying disadvantageous decision-making in each condition.

To conclude, evidence from neurodegenerative diseases speaks against the idea of a simple dual process accounting for intertemporal choices (McClure et al., 2004) and confirms the involvement of a complex interplay of mechanisms centered on a valuation process that can be optimized upon detection of conflict between options. Burning issues for research on delay discounting in neurodegenerative diseases are summarized in Box 2. The main challenge of using neurodegenerative diseases as models to study delay discounting mechanisms is that several cognitive aspects and brain regions are concomitantly modified in each disease. However, we can use the overlapping and contrasting features between conditions to further investigate the roles of specific cognitive processes / brain regions in discounting. Further comparisons are needed between discounting performances of PD, AD and FTD, in particular using different adapted versions of the task and combined MRI analysis, to better isolate the roles of the different cognitive mechanisms in each condition. A key element in comparing PD and AD-FTD is the disease stage, given that PD can be cognitively preserved longer than AD and FTD, which may represent a burden for the interpretation of our results. For clinical practice, it is unlikely that discounting performance could serve as a standalone diagnostic tool of neurodegenerative diseases. However, the delay discounting task could contribute to the early prediction of neurodegeneration cerebral changes. It could also predict impulsivity symptoms in PD and refine the diagnosis of dementia (e.g., AD vs bvFTD, behavioral subtypes of FTD). Next steps towards the implementation of the delay discounting task into clinical practice in the field of neurodegenerative diseases are summarized in Box 2. One of the critical steps will be the development of clinical scales based on delay discounting assessment. Along with the behavioral measure, using whole-brain neuroimaging patterns predicting delay discounting in individual patients could also be explored as an innovative path towards personalized diagnosis and treatment.

Declaration of Competing Interest

The authors have no competing interests to declare.

Data Availability

No data was used for the research described in the article.

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