Neurocognitive Signatures of Parkinson's and Alzheimer's Disease

Ph.D. Dissertation

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TABLE OF CONTENTS

ABBREVIATIONS

AD – Alzheimer's disease

ANCOVA – analyses of covariance

ANOVA – analyses of variance

CBDS – corticobasal degeneration syndrome

CDT – Clock Drawing Test

DDS – dopamine dysregulation syndrome

DRS – Dementia Rating Scale

FTD – frontotemporal dementia

FTD-bv – frontotemporal dementia behavioral variant

GDS – Global Deterioration Scale

HAM-A – Hamilton Anxiety Rating Scale

HAM-D – Hamilton Depression Rating Scale

HSD – Honestly Significant Difference test

MANOVA – multivariate analyses of variance

MMSE – Mini - Mental State Examination

MRI – Magnetic Resonance Imaging

NINCDS-ADRDA – National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

PA – progressive aphasia

PD – Parkinson's disease

PET – positron emission tomography

PNFA – primer non-fluent aphasia

PSP – progressive supranuclear palsy

SD – semantic dementia

TCI - Temperament and Character Inventory

TPQ – Tridimensional Personality Questionnaire

UPDRS – Unified Parkinson's Disease Rating Scale

WAIS-R – Wechsler Adult Intelligence Scale

1. INTRODUCTION

1.1. The importance of common neurodegenerative diseases

Neurodegenerative diseases comprise one of the major public health concerns in our aging population. According to the data from the EURODEM study, the incidence of dementia ranges between 0.6-8.2/100 individuals in the age range of 70-90 years, whereas the prevalence is 2.9-30.8% (Launer et al., 1999). The exact etiology and pathophysiology remain elusive, but large-scale studies identified several risk factors that may contribute to the diseases. These general risk factors include various genetic polymorphisms, gene copy number variations, increasing age, poor education, endocrine diseases, oxidative stress, inflammation and infection, hypertension, diabetes, smoking, head trauma, depression, vitamin deficiencies, nutritional problems, and toxic environmental exposure (Launer et al., 1999).

The proper clinical diagnosis of neurodegenerative diseases is often difficult given the large overlap in signs and symptoms, although in more than 75% of cases the clinical diagnosis is confirmed by postmortem examination (Mok et al., 2004). The situation is even more complex, because neurodegenerative diseases may overlap and co-exist at the molecular pathological level (Armstrong et al., 2005). Some experts suggest a neuropathological classification of diseases instead of clinical symptoms, such as alpha-synucleinopathies (e.g., Parkinson's disease), amyloidopathies (e.g., Alzheimer's disease), and taupathies (e.g., fronto-temporal dementia) (Jellinger, 2008).

In the clinical practice, physicians focus on signs and symptoms and their progression; the classification systems of diseases is based on expert consensus bearing the sign of subjectivity, and we have to face with the fact that definitive biomarkers are still missing from the everyday practice. One possible solution is the standardized application of neuropsychological tests measuring the functional integrity of neuronal circuits, possibly with markers from peripheral blood and brain imaging.

Here, we focus on the neurocognitive bases of two common disorders, Parkinson's and Alzheimer's disease (PD and AD). PD is traditionally considered as a *motor disorder* characterized by intact or mildly affected cognitive functions until the latest stages of the disease (Lees et al., 2009). The cognitive deficit is predominantly

described as an anomaly of processing speed, attention, and executive functions, establishing the concept of *subcortical dementia* that occurs in approximately 20% of cases. PD dementia must be differentiated from Dementia with Lewy Bodies in which we can observe severe fluctuations in alertness and attention, recurrent visual hallucinations, and parkinsonian motor symptoms. In this disorder, cognitive problems related to cortical functions occur earlier, and therefore easier to confuse with AD (Korczyn and Reichmann, 2006; Selikhova et al., 2009). When memory, language, and visuo-spatial functions are predominantly affected, we can define the condition as a *cortical dementia*. This classification is nevertheless oversimplified and can hardly be considered valid today. Both AD and PD are common in the elderly, and patients with PD who develop dementia may have AD as well (Bonelli and Cummings, 2008).

In the forthcoming experiments, we will present data regarding three novel aspects of PD and AD

1. We explore specific cognitive deficits and personality changes in the early-stage of PD, with a special reference to reinforcement learning guided by positive and negative feedback. The effect of dopamine receptor agonists on these early non-motor changes will be investigated, showing how these drugs shift the balance of reward and punishment sensitivity.

2. We show that in early AD the cognitive deficit is not generalized. However, even successful feedback-guided stimulus-outcome learning results in rather context-specific memory traces that can not be applied in new retrieval situation in a flexible way.

3. Finally, we explore how more traditional clinical neuropsychological tests of visuo-spatial orientation and constructive abilities may serve to differentiate AD from other types of dementia.

1.2. Beyond the motor symptoms: reinforcement learning in PD

1.2.1. Basic pathology: from molecules to cognition

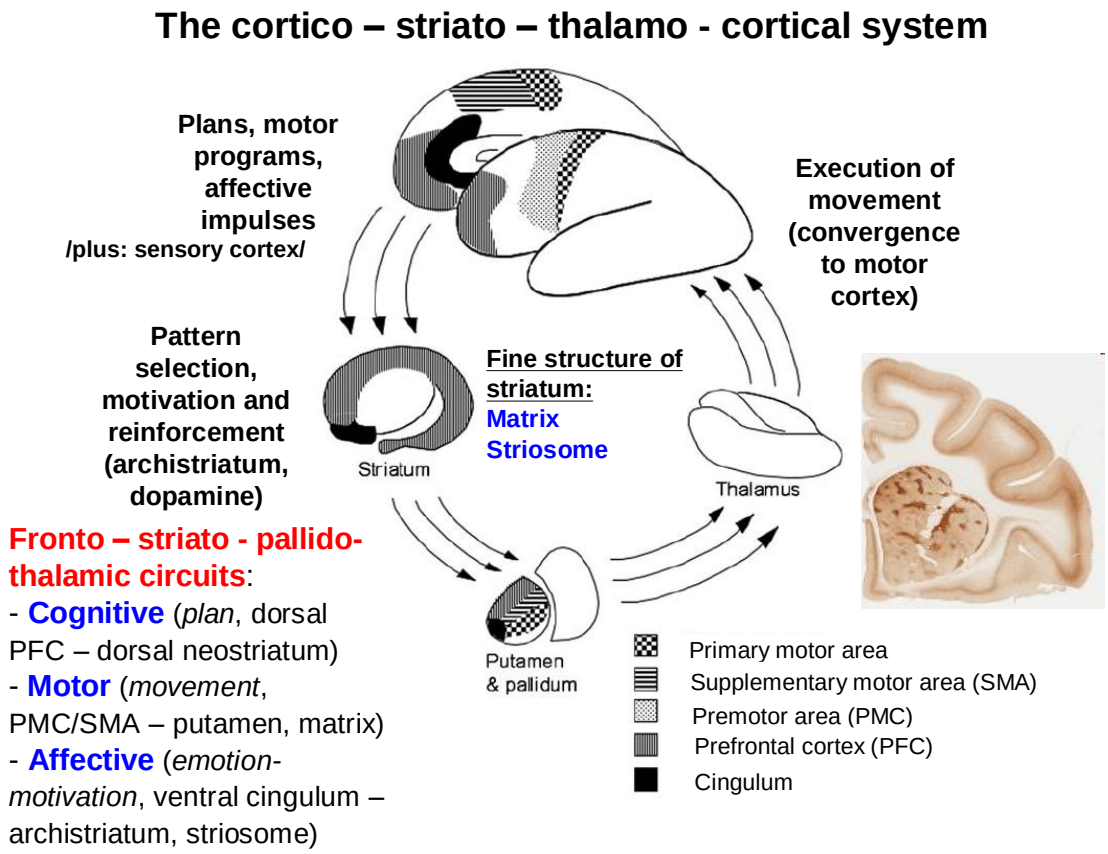
PD was described by James Parkinson in 1817, although a similar symptomatic delineation can be found in the work of Ferenc Pápai Páriz from 1690 with all four cardinal symptoms: resting tremor, rigidity, bradykinesia, and gait disturbances (Bereczki, 2010). The classic neuroanatomical definition of PD is based on the loss of neuromelanine-positive dopaminergic cells in substantia nigra pars compacta, leading to the disturbance of the nigrostriatal pathway (Lees et al., 2009). Neuronal loss may be induced by accumulated alpha-synuclein in these cells that comprises the core of the Lewy-bodies. Damaging *alpha-synuclein* may occur via phosphorylation by intracellular kinases, truncation by proteases, modification by free radicals, reactive nitrogen species, toxins, overproduction (gene duplication), and decreased elimination by parkin and synphilin (Venda et al., 2010). However, alpha-synuclein is not the sole player in mitochondrial damage and abnormal ubiquitine-proteosomal functions; other relevant factors are Parkin (PARK2), PINK1 [phosphatase and tensin homolog-induced putative kinase 1] (PARK6), DJ-1 (PARK7), LRRK2 [leucine-rich repeat kinase 2] and dardarin (PARK8) (Mellick et al., 2010). From our point of view, alpha-synuclein and its interactive proteins are especially important because this molecule, acting as a presynaptic regulator of dopamine release, may bridge neurodegeneration and cognition (Kéri et al., 2010).

Regarding the functional localization of PD, the hypothesis of selective nigrostriatal dysfunction seems to be problematic given that it can hardly explain several non-motor symptoms of PD: olfactory, sleep, and vegetative abnormalities, blunted affect, changes in personality traits (e.g., decreased novelty seeking and increased neuroticism), and atypical responses to dopaminergic medications in some patients (e.g., impulse control disorders and psychotic symptoms) (Bassetti, 2011). Consistent with post-mortem studies showing that the loss of dopaminergic neurons in the substantia nigra is just an intermediate step in neurodegeneration, Jubault et al. (2009) demonstrated in vivo imaging evidence for an early volume loss in the medulla

oblongata/pontine tegmentum, which is followed by neurodegeneration in substantia nigra/amygdala, and then in the cortex.

Although dopaminergic deficit is a hallmark of PD, the loss of this neurotransmitter is not evenly distributed in the striatum. Specifically, there is a more pronounced reduction of dopamine in the dorsal than in the ventral striatum (Kish et al., 1988). Therefore, therapies that restore dopamine level in the dorsal striatum result in dopamine "overdose" in the ventral striatum, which may lead to impaired performance on some cognitive tasks (Gotham et al., 1988; Cools et al., 2001, 2003; Shohamy et al., 2006; Jahanshahi et al., 2010; MacDonald et al., 2011) and in some cases to psychotic symptoms, including hallucinations and delusions (Mehler-Wex et al., 2006; Maia and Frank, 2011). At the same time, there is evidence that dopaminergic therapy enhances learning from reward signals and decreases learning from punishment signals in PD (Frank et al., 2004, 2007; Cools et al., 2006; Graef et al., 2010; Kobayakawa et al., 2010), and the ventral striatum plays a crucial role in reinforcement learning (Yin and Knowlton, 2006). ***Figure 1*** shows a renewed scheme of the cortico-striatal system that clearly indicates the non-motors functions of this complex system. The effect of dopamine receptor agonists on non-motor functions in PD was explored in first series of our studies.

Figure 1.



Based on Bradshaw and Shepard, 2000

Pathways from the frontal cortex project to different regions of the striatum that in turn give output to the putamen and pallidum, which send afferents to the thalamus and cortex. Frontal regions are responsible for the processing of plans (dorsolateral region), complex motor programs (premotor and supplementary motor area), and affective/social representations (ventral frontal and cingular region). In the striatum neuronal activation patterns are selected and modified according to the current motivational state and reinforcers. This process is regulated by dopamine in the archistriatum (ventral striatum or nucleus accumbens). Striosomes, which are rich in acetylcholinesterase activity, are important in affective functions, whereas the matrix is more closely related to motor functions.

1.2.2. Reinforcement learning in PD

There are multiple lines of evidence that the striatum and its dopaminergic projections from the midbrain are important for learning to predict rewarding outcomes (Schultz, 2007). This reward prediction signal is critical for tasks during which responses to salient stimuli are modified by feedback. Given the well-known loss of dopaminergic signals in the striatum of PD, it is expected that PD patients show impairments on tasks requiring feedback-based reinforcement learning (Yin and Knowlton, 2006).

Animal studies indicate that neurons in the mesencephalic dopaminergic centers show phasic excitatory responses following primary rewards and after intensive and unexpected sensory stimuli. There are three groups of these neurons: A9 (pars compacta of substantia nigra), A10 (ventral tegmental area) and A8 (dorsolateral substantia nigra). A8-A10 cells project their axons to the dorsal and ventral striatum, as well as to the dorsolateral and ventromedial frontal cortex. Interestingly, these neurons are transiently inhibited when reward is omitted or when conditioned stimuli are presented that predict the absence of reward (Schultz, 2007).

Dopamine, a classic neurotransmitter related to PD, psychosis, and mood disorders, seems to regulate the functional connectivity of striatal, limbic, and prefrontal areas during conditioning and reinforcement learning, and enhances responses to salient stimuli regardless of their hedonic value, possibly acting in the ventral striatum (Berridge, 2007). The most likely scenario is that some mesencephalic dopamine neurons encode motivational valence (reward), whereas others encode motivational salience. Both valence and salience encoding neuronal populations are facilitated by novelty and alerting signals in order to detect important environmental objects and events (Bromberg-Martin et al., 2010). Therefore, phasic dopamine responses may serve as a "teaching signal" during reinforcement learning. Interestingly, similar mechanisms have been revealed in humans using high-resolution functional neuroimaging techniques during various laboratory tasks, which provide unique insight into the organization of human dopaminergic cell groups in the mesencephalon (Düzel et al., 2009).

In a seminal study, Knowlton et al. (1996) compared amnesic patients with hippocampal damage and nondemented patients with PD on a probabilistic classification task in which participant acquired which of two outcomes would occur on

each trial (a pattern of figures predict rain or sunshine). Surprisingly, amnesic patients performed well on this feedback-guided task despite the fact that they had severe declarative memory impairment and hardly were able to consciously recall the stimuli. Lesions to the prefrontal cortex did not affect learning, too. However, PD patients failed on the feedback learning phase, but showed intact declarative memory for the figures (Knowlton et al., 1996).

It is especially intriguing how PD patients exhibit compensatory brain activation during feedback-based reinforcement learning tasks. Patients with PD show less activation in the striatum and greater activation in the prefrontal cortex and medial temporal lobe, which may indicate that they use an explicit memory strategy during a reinforcement learning procedure (Moody et al., 2004). Overall, it is concluded that the neostriatum is essential for the gradual and incremental learning of associations. These findings were clearly pioneered by Saint-Cyr et al. (1988) who demonstrated a similar double dissociation in PD and amnesia with more traditional test procedures.

However, this type of gradual associative learning depends on L-dopa medication, which enhances global dopamine level and impairs certain types of feedback-based learning, presumably because of the "overdosing" of dopamine in brain areas less affected in PD, i.e.. the ventral striatum (Cools et al., 2001, 2003; Shohamy et al., 2006). The biased effect of dopamine replacement may improve motor functions and cognitive flexibility, but, at the same time, may induce impulsivity and decreased performance on tasks involving negative feedback-based learning (Cools et al., 2001, 2003; Shohamy et al., 2006).

Current models suggest that the ventral striatum underlies learning of stimulus associations, whereas the dorsal striatum is responsible for the processing of competing patterns during response selection. In decision making tasks, dopamine replacement therapy impairs stimulus-stimulus relation learning, but facilitates the selection of appropriate responses when conflicting informations must be resolved. This is consistent with activation of the ventral vs. dorsal striatal regions during stimulus-stimulus association learning and response selection, respectively (MacDonald et al., 2011).

Frank et al. (2004, 2007) demonstrated that PD patients off L-dopa are better at learning from punishment (negative outcome, e.g. losing points in a game) than from

reward (positive outcome, e.g. winning points); L-dopa reverses this pattern of task performance, enhancing learning from reward at the expense of punishment. Cools et al. (2006) confirmed these findings using a feedback-based reversal learning task. In the study of Cools et al. (2006), medication-induced deficit for punishment was particularly pronounced in patients who received the dopamine D3 receptor agonist pramipexole. D3 dopamine receptors are densely expressed in the ventral striatum, and it is possible that the stimulation of these receptors leads to decreased punishment sensitivity. Alpha-synuclein is a presynaptic negative regulator of dopamine release (Venda et al., 2010), and individuals with copy number variations of the alpha-synuclein gene, leading to the over-expression of the protein, display pronounced reward learning deficits well before the emergence of motor symptoms (Kéri et al., 2010).

Overall, models describing the effect of dopaminergic medication on reinforcement learning in PD do not take into consideration a couple of key factors. First, in PD it is possible that tonic increase of dopamine after L-dopa administration over-rides phasic release of dopamine, which is the key „teaching signal" for learning. Second, it is important that the selective stimulation of dopamine receptors may have a substantially different effect compared to L-dopa. Such kind of receptor-specific stimulation occurs in the case of dopamine agonist administration.

The first class of these drugs includes ergolinic dopamine agonists, such as bromocriptine or pergolide, whereas later non-ergolinic drugs, such as pramipexole and ropinirole, were marketed. Ergoline agents bind with high affinity to D2 receptors but also bind to D1, adrenergic, and serotonin receptors. Non-ergolines have a higher selectivity to D2 and D3 receptors; pramipexole shows an especially strong affinity to D3 receptors (Kvernmo et al., 2006). D3 receptors are prominently expressed in the ventral striatum, and therefore drugs stimulating this receptor may modulate reward-related learning processes (Cools et al., 2006). Drugs binding to D1 receptors stimulate the direct cortico-striato-thalamic pathways, which are considered to act as a stimulatory pathway for reinforcement learning providing "go" signals (Frank et al., 2004). However, the exact receptor-specific effect on learning has not been studied and its clinical relevance is not clear, too.

In addition to the classic side effects of dopaminergic medications, such as nausea, psychotic symptoms, and orthostatic hypotension, dopamine agonists also

induce daytime somnolence, impulse-control disorders (drug addiction, gambling, overactive sexual behavior), and heart valve fibrosis in some patients. It is not clear whether dopamine agonists have a disease-modifying, i.e. neuroprotective effect and whether these drugs are more effective in the treatment on non-motor symptoms such as depression (Perez-Lloret and Rascol, 2010). This latter symptom of PD may be directly related to reinforcement learning.

1.2.3. Is altered sensitivity to reinforcers related to personality changes in PD?

In the previous section, we delineated a mechanistic model for dopaminergic functions in the mesencephalic-striatal system for reinforcement learning. However, dopamine may play a crucial role in higher-level human functions, such as patterns of emotional reactions, attitudes, and cognitive schemas comprising the multidimensionality of human personality. The most deeply investigated dopamine-related personality trait, in which norepinephrine could also be important, is novelty seeking including exploratory excitability, impulsiveness, extravagance, and disorderliness, as measured by the Temperament and Character Inventory (TCI) (Cloninger, 1994). There are numerous case reports suggesting rigid, punctual, and introverted personality in PD, but the results are mixed and non-conclusive (Menza, 2000; Jacobs et al., 2001; Tomer and Aharon-Peretz, 2004). In accordance with decreased dopaminergic transmission, some reports suggest decreased novelty seeking in PD (Menza, 2000), but other authors emphasize increased scores on harm avoidance (anticipatory worry, fear of uncertainty, shyness, and fatigability), which may be related to PD-associated depression (Jacobs et al., 2001). Premorbid personality may be especially important, because it may affect vulnerability to dopamine dysregulation syndrome induced by medications.

Krebs et al. (2009) investigated the neuronal correlates of novelty seeking and reward dependent personality traits. Using a reinforcement learning task with monetary incentives, functional magnetic resonance imaging hemodynamic responses were registered from the substantia nigra/ventral tegmental area, nucleus accumbens, and hippocampus. Novelty seeking was positively correlated with activation in the substantia nigra/ventral tegmental area elicited by new stimuli that did not predict

reward, whereas reward-dependence was related to activations elicited by novel cues that predicted reward. The responses of these mesencephalic regions to novelty and reward are differentially associated with novelty seeking and reward-dependence. Persons with higher novelty seeking scores tend to respond to new stimuli even when it is not associated with reward, and in their case less reward is necessary to enhance hippocampal activation and to boost their memory for new stimuli. It is notable that midbrain dopamine autoreceptor density is negatively correlated with novelty seeking (Zald et al., 2008).

An important limitation of the literature regarding both reinforcement learning tasks and personality assessment is that studies include chronic elderly patients with PD receiving multiple medications, and many of these patients exhibit multiple neuropsychiatric co-morbidities from mood disorder to psychotic symptoms and generalized cognitive decline. Longitudinal follow-up studies are missing from the literature. Finally, it is unknown how sensitivity to reward and punishment in laboratory tasks is related to complex personality traits. Young-onset PD may be an especially important condition, because it is associated with slower progression of motor symptoms, longer disease course with spared cognitive function, but sometimes an earlier appearance of motor fluctuations, dyskinesias, and psychiatric symptoms (Schrag and Scott, 2006). The pathology is more circumscribed than in late-onset PD, but, paradoxically, in some cases cell loss in the substantia nigra is very definitive (Gibb and Lees, 1988).

1.3. The mirror image of parkinsonian cognition in AD

1.3.1. The medial temporal lobe and beyond

The pathological process resulting in AD and first hitting the medial temporal lobe is still not clear, but it is at least partly different from that observed in PD. AD is also considered as a protein misfolding disease (proteopathy); in this case the key protein is not alpha-synuclein, as for PD (although Lewy bodies can occur in AD), but the basic alteration may be the accumulation of abnormally folded amyloid-beta and tau

proteins. Amyloid plaques consist of 39–43 amino acids peptides. In AD hyperphosphorylation of microtubule-associated protein tau causes abnormal changes in cellular transport (Finder, 2010). From the amyloid small toxic fragments may be released (amyloid-derived diffusible ligands) that bind to prion protein in the cell membrane and disrupt synapses (Laurén et al., 2009). This mechanism may explain how neurodegenerative process is spreading in the brain.

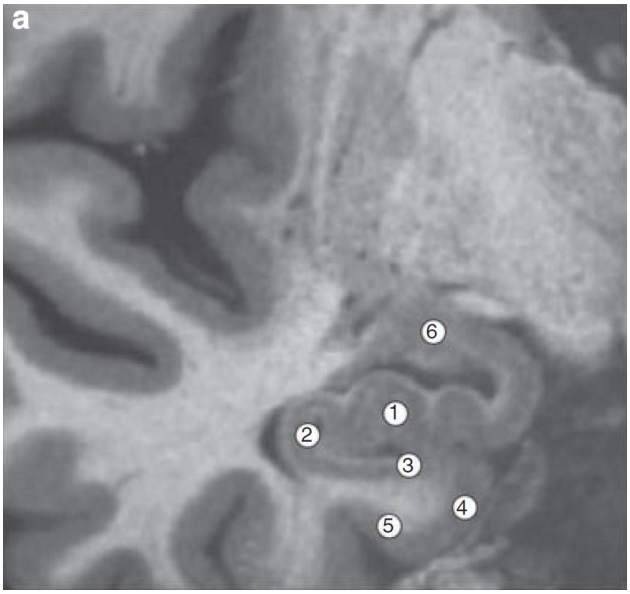
What are the neuropsychological consequences of this degenerative process? If we reconcile the Saint-Cyr et al. (1988) and Knowlton et al. (1996) experiments, it is not difficult to make inferences from amnesia to AD, given that the earliest stage of AD is dominated by declarative memory dysfunctions, although the attentional system may be affected even earlier (Parasuraman et al., 2000). Nevertheless, patients with early AD show superior performances on feedback-based stimulus-outcome learning tasks in which PD patients are impaired (Klimkowicz-Mrowiec et al., 2008). Declarative memory impairment in AD is linked to the atrophy of the medial temporal lobe, with a special reference to the entorhinal cortex and later the hippocampus proper. However, the scenario seems to be more complex. In a systematic quantitative meta-analysis of structural and functional neuroimaging studies including 1351 patients and 1097 healthy controls, Schroeter et al. (2009) found that in early AD the trans-entorhinal and hippocampal regions are decreased in volume, whereas metabolism and blood flow are reduced in the inferior parietal lobules and precuneus. Atrophy in the trans-entorhinal cortex and hippocampus, as well as hypometabolism/hypoperfusion in the inferior parietal lobules predict progression from amnestic mild cognitive impairment to AD. In fully developed AD, the medial frontal cortex and its connection with the thalamus is also disrupted.

In 917 patients with mild cognitive impairment, a prodromal form of AD, and in 809 healthy controls, Nickl-Jockschat et al. (2011) showed grey matter reduction in bilateral amygdala and hippocampus, extending to the left medial temporal pole, thalamus, and bilateral precuneus. A voxel-wise analysis revealed a correlation between grey matter loss and progressive cognitive deficits in the right hippocampus and amygdala, and in the left thalamus. ***Figure 2*** shows the structural organization of the medial temporal lobe and related brain regions.

How do these structural alterations affect cognition? Using functional magnetic resonance imaging, de Rover et al. (2011) demonstrated differential hippocampal activation in mild cognitive impairment and control groups during the paired associates learning task: patients displayed higher activation than controls at low memory loads and less at higher loads. Importantly, this functional impairment was confined to the hippocampal region, consistently with the structural alteration of it (grey matter reduction). Hanseeuw et al. (2011) showed that declarative associative memory correlates with hippocampal volume.

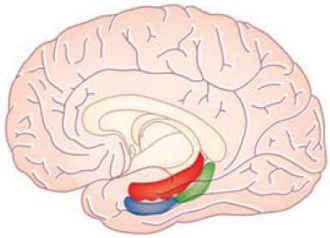
Impaired reversal of stimulus context, which inversely correlates with right hippocampal volume, is also a characteristic alteration in mild cognitive impairment and early AD (Levy-Gigi et al., 2011). However, it does not depend on the valence of the feedback used in the task: it is observed both when previously negative outcomes became positive and when previously positive outcomes became negative. The valence-independence of context reversal learning dysfunction may indicate normal affective processing and intact ventromedial frontal cortex, as well as intact ventral striatal functions (Levy-Gigi et al., 2011) in contrast to PD where the balance between positive and negative outcome is disturbed during reversal learning (Cools et al., 2006).

Figure 2. The structural organization of the medial temporal lobe



1. **CA3/dentate gyrus**
2. **CA1**
3. **Subiculum**
4. **Entorhinal cortex**
5. **Perirhinal cortex**

CA = Cornu Ammonis



Hippocampus
Parahippocampal area
Ento-/perirhinal cortex

Based on Eichenbaum et al., 2007

The proper functional and structural delineation of the medial temporal lobe is still a matter of debate. The analysis of 210 neuropsychologically characterized individuals demonstrated that delayed retention is associated with the basal metabolism of the entorhinal cortex, whereas recognition performance is associated with metabolism of the dentate gyrus (Brickman et al, 2010). Regarding episodic memory, it has been proposed that distinct items (e.g., objects and persons) are represented in the perirhinal and lateral entorhinal cortex, whereas spatial context of the item is processed in the parahippocampal and medial entorhinal cortex (Eichenbaum et al., 2007). These latter structures may be especially vulnerable in early AD. Mueller et al. (2010) provided evidence that the CA1-2 zone is better than the total hippocampal volume for discrimination between healthy controls and persons with early memory disturbances. The hippocampus may be responsible for placing items in spatial context (Eichenbaum et al., 2007), which is impaired in early AD.

1.3.2. Novel functions of the medial temporal lobe and AD: the acquired equivalence paradigm

AD is traditionally characterized by a severe dysfunction of declarative memory, which refers to the conscious recollection of facts and events. This deficit is associated with the pathology of the medial temporal lobe, including the hippocampus, in the early stage of the disease (deToledo-Morrell et al., 2007). Although traditional associative learning, such as remembering face-name or object-place pairs, is related to the hippocampal region as a sensitive marker of AD (Sperling, 2007), recent evidence suggests that not all types of associative learning require medial temporal lobe involvement. This is especially true when associations are acquired via feedback during extended and gradual training sessions. Previous studies assessed non-demented elderly individuals with and without hippocampal atrophy on stimulus-response associative learning tasks (Myers et al., 2002, 2003). Surprisingly, individuals with atrophy of the medial temporal lobe were able to learn stimulus-response associations and were able to perform a series of object discriminations when acquisition was gradual and guided by feedback after each decision. However, they were impaired on a generalization task in which familiar features and objects were recombined. PD patients showed the opposite pattern of performance: they required more trials to learn the associations but showed intact generalization (Myers et al., 2002, 2003).

Nagy et al. (2007) tested never-medicated PD patients and individuals with amnestic mild cognitive impairment on a chaining stimulus-response associative learning task. In the training phase of the task, each link in a sequence of stimuli leading to reward is trained step-by-step using feedback after each decision until the complete sequence is learned. The computer-assisted task was to find a way out from a chain of four rooms in which only one door was open. In the probe phase of the chaining task, the context of stimulus-response associations must be used (the position of the associations in the sequence). Patients with PD showed impaired learning during the feedback-guided training phase of the task, but their performance was spared in the context-dependent probe phase. The opposite was observed in mild cognitive impairment in which medial temporal lobe functions are disturbed: these patients showed intact learning during the feedback-based training phase, but their performance was impaired in the probe phase when context (which door is open in each room) must be used in a flexible manner (Nagy et al., 2007).

The results of these studies suggest that the hippocampal region may not be critical for simple feedback-guided stimulus-response associative learning, but it is indispensable for the generalization and flexible application of this knowledge. This raises the possibility that generalization deficit may be a sensitive marker of medial temporal lobe pathology and may be an early indicator of risk for cognitive decline in AD.

One particularly intriguing form of generalization is *acquired equivalence*, which is a well-known paradigm in traditional animal behavior research (Ellis et al., 1964). There are two basic forms of acquired equivalence. In the first case, rats are trained with two visual stimuli (X and Y) followed by the same outcome (food) or by different outcomes (food and no food). After this conditioning procedure, X is paired with an electric shock and the generalization of conditioned suppression to X is determined. Suppression to stimulus X is larger when X and Y were both followed by food than when they had different outcomes in the conditioning phase (Honey and Hall, 1989). In the second from of acquired equivalence, three stimuli (X, Y, Z) are used. In one group of animals, two stimuli are paired with food and one (Z) is not followed by any reinforcement. In the control group, Z is reinforced by food and the other two stimuli are not reinforced. In this paradigm, animals respond equivalently to stimuli if their reinforcement history is similar, that is, they were followed by food or not (Honey and Hall, 1989).

Coutureau et al. (2002) investigated the neuronal basis of acquired equivalence. Excitotoxic lesion was used to impair the entorhinal cortex or the hippocampus proper in rats before training in a reinforcement schedule. In two environmental contexts (A and B), stimulus X was followed by food, whereas stimulus Y was not reinforced. In two other contexts (C and D), Y was followed by food and X was non-reinforced, reversing the contingencies. After this conditioning, rats received food ad librium in context A but not in context C. As expected, control rats without brain lesion showed more activity in context B than in context D, which is a manifestation of acquired equivalence. A similar behavior was observed after the lesion of the hippocampus proper, but not after the lesion of the entorhinal cortex when acquired equivalence was severely disrupted.

In summary, acquired equivalence is a phenomenon in which prior training to treat two stimuli as equivalent with similar outcomes increases generalization between them, even if the stimuli are perceptually very dissimilar. Acquired equivalence learning is markedly impaired in individuals with the atrophy of the hippocampal region (Myers et al., 2003). The question is open how patients with early AD are able to learn stimulus-response associations and how they are able to generalize this knowledge in an acquired equivalence situation and in other conditions that require conscious access and flexibility in stimulus-response associations.

1.3.3. Visuospatial abilities in AD and other dementias

The clock drawing test (CDT) is a widely used clinical measure to screen for dementia, especially AD (Pinto et al., 2009). The CDT has several advantages in the clinical practice: the procedure is quick, easy to administer, well tolerated by patients, straightforward to score providing results independent of culture (Shulman, 2000). The CDT taps several cognitive functions including planning, visual memory, graphomotor ability, and visuospatial and constructive skills (Freedman et al., 1994).

Despite the widespread application of the CDT in clinical populations, its neuronal correlates are less clarified. Tranel et al. (2008) investigated 133 patients whose lesions were localized in various parts of the neocortex and white matter tracts. Impairments on the CDT were associated with damage to the right supramarginal gyrus and left inferior frontal-parietal opercular cortices. Visuospatial errors were more frequent in patients with right hemisphere damage, whereas time setting errors were observed in patients with left hemisphere lesions.

However, correlation with lesion localization may be affected by the scoring system used during the assessment of the patients. Regardless of the scoring method, CDT scores were positively correlated with grey matter volume in the right parietal lobe. Shulman's CDT scores were positively correlated with grey matter volume in the bilateral posterior temporal lobes, and Rouleau's scores were correlated with the right posterior superior temporal lobe (Matsuoka et al., 2011).

The CDT is suitable for the discrimination of AD from dementia with Lewy bodies and PD (Cahn-Weiner et al., 2003). According to some authors, CDT is one of

the best methods to make a differentiation between AD as a cortical dementia and other dementias with subcortical pathology. However, data are sometimes controversial in the literature. Fukui et al. (2009) directly tested the hypothesis that subcortical cognitive impairment and AD can be differentiated by using visuospatial tasks. These authors assessed 60 patients with AD and 63 patients with extrapyramidal diseases with cognitive impairment with the clock drawing/reading/matching tests and Frontal Assessment Battery. In the mild stage of the disease, results from all measures were similar in AD and patients with subcortical pathology. However, in the moderate-severe stage, clock drawing scores were lower in the case of subcortical pathology as compared with AD. The results raise the possibility that in the mild stage of the disease, visuospatial functions are not sufficiently sensitive to differentiate patients with different types of dementia. The fact that subcortical pathology was also associated with frontal symptoms, which can be interpreted by the disruption of fronto-striatal loops, further complicates the situation raising the possibility that executive dysfunction may also contribute to abnormal CDT performance. This controversy should be elucidated by the investigation of dementia types with direct frontal involvement.

Cosentino et al. (2004) demonstrated that in the command version of the CDT, errors on the Time subscale correlated with impaired executive functions, and in the copy condition errors on the Perseveration/Pull to Stimulus subscale showed a similar correlation. In the command condition, when white matter tracts are disrupted by ischemic lesions, performance is similarly impaired to that observed in PD, which is even more prominent than that found in AD. Therefore, large-scale interconnected fronto-striatal network may be crucial, providing evidence for the hypothesis that executive functions are important for the successful completion of the CDT.

To elucidate the proper neuronal correlates of the CDT, it is essential to choose the right control condition. For example, in the test condition subjects are asked to draw the hands of a clock according to the time presented acoustically. In the control task, they draw horizontal and vertical lines and recite the numbers presented acoustically. Functional magnetic resonance imaging revealed activation in the test condition relative to the control condition in the bilateral posterior parietal cortices with right-sided dominance, bilateral dorsal premotor areas, left pre-supplementary motor area, left ventral prefrontal cortex, left precentral gyrus, and bilateral cerebellum. The posterior

parietal cortex and the dorsal premotor area yielded the strongest activation, and it was consistent across each participant (Ino et al., 2003).

Frontotemporal dementia (FTD) has an estimated prevalence of 12.5% of autopsied cases (Brun, 1987), but it is not a homogeneous group. At least three subtypes are differentiated: behavioral variant, progressive non-fluent aphasia, and semantic dementia. Similarly, FTD is not a homogeneous group at the neuropathological level. At least three main subtypes can be differentiated: (1) classic neuropathology of Pick's disease with 3-repeat tau protein inclusions, (2) tau-positive pathology other than the 3-repeat variant (e.g., FTDP-17, corticobasal degeneration, progressive supranuclear palsy), (3) TDP-43/ubiquitin positive and tau-negative frontal degeneration with or without motor neuron loss (Galaritois et al., 2005; Kertesz et al., 2005; Frank et al., 2008).

Executive dysfunctions are most prominent in the behavioral variant of FTD, which is characterized by attentional dysfunction, behavioral inhibition or release, perseveration, utilization behavior, and various social cognitive impairments. It is important that patients with FTD show relatively preserved medial temporal lobe functions, which is the traditional discriminative sign from AD. Behavioral and language impairments appear earlier in FTD than in AD (Kertész and Munoz, 1998; Bozoki and Farooq, 2009).

Although the CDT is widely used in populations with different types of dementia, it is less clear how it is related to FTD vs. AD. Moretti et al. (2002) showed that FTD patients had higher scores than AD patients on a 10-point scoring system. Rating was confined to overall CDT scores rather than detailed error analysis among the groups. Rascovsky et al. (2002) arrived at the same conclusion and found that pathologically confirmed FTD patients scored higher than AD patients, but only overall differences were examined. Given the complex nature of the CDT, a detailed qualitative error analysis may reveal more substantial differences across groups.

2. SPECIFIC AIMS

The following series of experiments had the following specific aims and hypotheses:

1. We investigated young, never-medicated patients with PD and a matched sample of PD patients who were on dopamine agonist therapy and did not receive any other drugs (e.g. L-dopa, antidepressants). Second, we followed-up the never-medicated sample after the initiation of dopamine agonists pramipexole or ropinirole (longitudinal, within-subject part of the study). We used a feedback-based probabilistic classification learning task that enabled us to investigate stimulus-response learning guided by positive and negative feedback (winning and losing virtual money). Results from this feedback-based task were compared with personality traits as measured by the TCI. Specifically, we were interested in novelty seeking and harm avoidance in unmedicated and medicated PD patients and their relationship with reward and punishment learning.

2. We investigated feedback-guided stimulus-response learning in early AD and tested the generalization and flexibility of these associations. The data analysis was focused on acquired equivalence and on the retrieval of associations in a free task context (non-directed card pairing) instead of instrumental responding.

3. The third specific aim was to test the discriminative power of the CDT regarding AD vs. FTD. The aim of our study was to examine both overall and specific error differences. We only examined the command condition of the CDT, because it is a more sensitive and cognitively demanding measure compared to the copy condition. The data analysis was focused on errors related to visuospatial difficulties and conceptual problems, as visuospatial skill can be relatively preserved in FTD patients, and AD patients are expected to display more conceptual errors.

3. METHODS

3.1. Participants

3.1.1. Participants in the reinforcement learning experiment

Participants were patients with idiopathic PD who had never received dopaminergic medications or who had recently begun medication with dopamine

receptor agonists. These patients were compared with healthy volunteers without a history of neurological or psychiatric disorders. The clinical and demographic data are shown in ***Table 1***. The mean dose of pramipexole (n=12) was 4.5 mg/day (range: 2.5-6.0 mg/day), the mean dose of ropinirole (n=10) was 5.5 mg/day (range: 2.0-7.0 mg/day). After baseline testing, never-medicated PD patients started dopamine agonist therapy and were followed-up for 12 weeks (pramipexole: n=14, mean dose at follow-up: 4.0 mg/day, range 2.0-6.0 mg/day; ropinirole: n=12, mean dose at follow-up: 5.5 mg/day, range: 2.0-7.5 mg/day). After this period, participants were re-evaluated.

The symptoms of PD were evaluated by the Hoehn-Yahr Scale (Hoehn and Yahr, 1967) and the Unified Parkinson's Disease Rating Scale (UPDRS) (Lang and Fahn, 1989). The Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A) were used to evaluate mood and anxiety symptoms, respectively (Mountjoy and Roth, 1982). The socioeconomic status was evaluated by the Hollingshead Four-Factor Index (Cirino et al., 2002). General intellectual abilities were determined using the revised version of the Wechsler Adult Intelligence Scale (WAIS-R) (Wechsler, 1981). All scales were administered by trained experts who were blind to personality measures, test performances, and medication status. All participants gave written informed consent and the study was approved by the institutional ethics board.

Table 1. Clinical and demographic characteristics of the participants

	Controls	Never medicated Parkinson's disease	Recently medicated Parkinson's disease
Number of participants (male/female)	20 (15/5)	26 (18/8)	22 (17/5)
Age (years)	45.3 (8.5)	44.8 (5.2)	45.3 (8.2)
Education (years)	13.7 (4.8)	13.3 (5.4)	14.4 (6.2)
Months since diagnosis*	–	3.2 (2.0)	8.8 (3.5)
Full-scale IQ (WAIS-R)	108.3 (10.0)	109.6 (11.7)	108.0 (13.9)
Socio-economic status (Hollingshead)	34.6 (13.0)	35.6 (14.7)	33.9 (16.8)

Novelty seeking*	20.8 (3.2)	17.0 (4.2)	25.0 (7.4)
Harm avoidance	15.8 (4.0)	15.5 (3.1)	15.5 (3.3)
Reward dependence	16.1 (4.4)	17.3 (4.2)	17.4 (4.1)
Persistence	4.2 (0.8)	4.0 (1.0)	4.1 (1.1)
No. of patients in Hoehn–Yahr Stage	–	1.0:4 1.5:2 2:18 2.5:1 3:1	1.0:2 1.5:2 2:15 2.5:2 3:1
UPDRS	–	30.8 (6.4)	27.5 (6.1)
HAM-D	–	4.2 (1.4)	4.6 (2.0)
HAM-A	–	3.1 (1.8)	3.3 (1.5)

Data are mean (standard deviation).

*Significant difference across group, P<0.05 (for details, see text)

3.1.2. Participants in the stimulus-learning experiment

Twenty-five patients with mild AD and 20 healthy elderly controls participated in the study. Patients and controls were matched for age, gender, and education. The diagnosis of probable AD was made according to the NINCDS-ADRDA criteria (McKhann, Drachman, Folstein, Katzman, Price & Stadlan, 1984). Participants were evaluated with the Mini-Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975) and Global Deterioration Scale (GDS) (Reisberg, Ferris, de Leon & Crook, 1982). Clinical information included medical history, laboratory tests, brain imaging findings (head magnetic resonance imaging [MRI]), neurological examination, and neuropsychological test results. Exclusion criteria consisted of vascular lesions on MRI scans and prior neurological and psychiatric disorders. The clinical and demographical data are shown in ***Table 2***.

Table 2. Clinical and demographical characteristics of the participants

	Controls (n=20)	Alzheimer's patients (n=22)
Age (years)	70.1 (4.8)	69.8 (6.9)
Male/female	12/8	15/7
Education (years)	13.7 (3.2)	13.6 (3.8)
MMSE	29.4 (0.7)	24.0 (1.3)
GDS	-	3.7 (0.5)

There were no significant differences between controls and Alzheimer's patients with the exception of the Mini-Mental State Examination (MMSE) scores (p<0.0001).

3.1.3. Participants in the visuospatial assessment

We analyzed clocks drawn by older individuals without dementia (*n* = 25) and patients diagnosed with FTD (*n* =36) and AD (*n* =25). The FTD group was composed of frontotemporal dementia behavioral variant (FTD-bv) (*n*=18), primer non-fluent aphasia (PNFA) (*n*=13), and semantic dementia (SD) (*n*=5) patients. All study participants were seen between 2003, when CDT according to the Rouleau et al. (1992) system became a regular part of clinical assessment, and early 2005 (***Table 3***). The AD patients all met the criteria for probable Alzheimer's disease according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984). The FTD sample fulfilled the Neary et al. (1998) and McKhann et al. (2001) criteria. The positive predictive value on autopsy based on the McKhann et al. (1984) and Neary et al. (1998) criteria have been shown to be greater than 80% (Bowler et al., 1998; Kertesz et al., 2005). The PNFA group included patients who were anomic, logopenic, and nonfluent. The SD group was diagnosed by the presence of a prominent comprehension deficit, naming difficulty, and asking the meaning of nouns and objects. All FTD patients were placed into FTD-bv, SD, and PNFA groups based on syndromes at the onset of illness. From the history provided at consultation 15 patients in the FTD-bv group had a behavioral syndrome at onset, 2 had dysexecutive problems observed around the home and at work, and 1 had a combination of both behavioral and dysexecutive symptoms at onset. At the time of the CDT, 3 FTD-bv patients had began to develop symptoms of progressive aphasia (PA), 2 had features of SD, and 1 had signs of motor neuron disease. Of the 5 SD patients, 3 had developed behavioral changes by the time of testing.

Table 3. Demographic characteristics, cognitive test results, and overall CDT scores of participants

	FTD (*n*=36) *M* (*SD*)	AD (*n*=25) *M* (*SD*)	Controls (*n*=25) *M* (*SD*)	Total Population (*N*=86) *M* (*SD*)	*p* value
Age (yrs)	65.14 (7.66)	78.76 (6.04)	65.36 (3.96)	69.16 (8.78)	b<.001
Education (yrs)	13.64 (3.74)	11.88 (4.77)	12.12 (2.93)	12.69 (3.9)	.17
Duration of	3.83 (2.02)	3.42 (2.12)			.45

illness (yrs)					
Gender (F:M)	18:18	10:15	13:12	41:45	.65
MMSE (maximum 30)	24.22 (3.98)	22.12 (1.92)	28.84 (1.07)	24.95 (3.86)	c<.001
DRS-2 (maximum 144)	113.21 (20.23)	113.25 (11.55)	139.44 (3.59)	121.63 (18.94)	a<.001
CDT (maximum 10)	7.74 (1.99)	5.48 (2.36)	9.54 (.58)	7.6 (2.4)	c<.001

Note. AD Alzheimer's disease, FTD Frontotemporal dementia.

a controls *versus* FTD, controls *versus* AD; **b** AD *versus* controls, AD *versus* FTD; **c** FTD *versus* controls, FTD *versus* AD, controls *versus* AD.

FTD patients with extrapyramidal disorders, such as corticobasal degeneration syndrome (CBDS) and progressive supranuclear palsy (PSP) that would interfere with their ability to perform the CDT, were excluded. This only resulted in the exclusion of two patients. One patient had FTD-bv as a primary syndrome with secondary and tertiary syndromes of CBDS and PA, respectively. The other patient had PNFA as a primary syndrome and PSP as the secondary syndrome.

The exclusion criteria for all patients included metabolic causes of dementia, history of drug abuse, alcohol dependence, serious psychiatric condition, neurological disorder such as stroke or closed head injury, a current major depressive episode, psychosis, acute mania, and bipolar disorder. Imaging was conducted on all patients to exclude other causes of dementia such as stroke or tumor. However, imaging was not used as a confirmatory diagnostic measure; diagnosis was based on the prior mentioned clinical criteria. Control data was obtained from the accompanying caregivers of patients.

The control group was selected to match the FTD groups in age and education. The inclusion criteria for controls consisted of no history of memory problems, age and education-adjusted scale score of nine or higher (normal range) on the second edition of the dementia rating scale (DRS-2; Jurica et al., 2001); and Mini-Mental State Examination (MMSE; Folstein et al., 1975) scores above age and education adjusted cut-off scores (Crum et al., 1993).

3.2.Tasks

3.2.1. Tasks in the reinfrocement learning experiment

Feedback-based probabilistic classification task

All participants were administered a computer-based probabilistic classification task (Bolikal et al., 2007). On each trial, participants viewed one of four images (***Figure 3***), and were asked to guess whether it belonged to category A or category B. For each participant, the four images were randomly assigned to be stimuli S1, S2, S3, and S4. A second set of similar images (S5-S8) were used for repeated testing (test-retest reliability based on the repeated testing of controls: r=0.76). On any given trial, stimuli S1 and S3 belonged to category A with 80% probability and to category B with 20% probability, while stimuli S2 and S4 belonged to category B with 80% probability and to category A with 20% probability (***Table 4***). Stimuli S1 and S2 were used in the reward-learning task. Two stimuli per valence were employed in order to balance category outcome frequencies, so that one stimulus in each task would be associated with each outcome. Thus, if the participant correctly guessed category membership on a trial with either of these stimuli, a reward of +25 points was received; if the participant guessed incorrectly, no feedback appeared. Stimuli S3 and S4 were used in the punishment-learning task. Thus, if the participant guessed incorrectly on a trial with either of these stimuli, a punishment of –25 was received; correct guesses received no feedback.

Figure 3. The feedback-based probabilistic classification task. (A) On each trial, the participant saw one of four stimuli and was asked whether this stimulus belonged to category A or B. (B) For some stimuli, correct responses were rewarded with visual feedback and 25 points winnings, whereas for others, incorrect responses were punished with visual feedback and loss of 25 points.

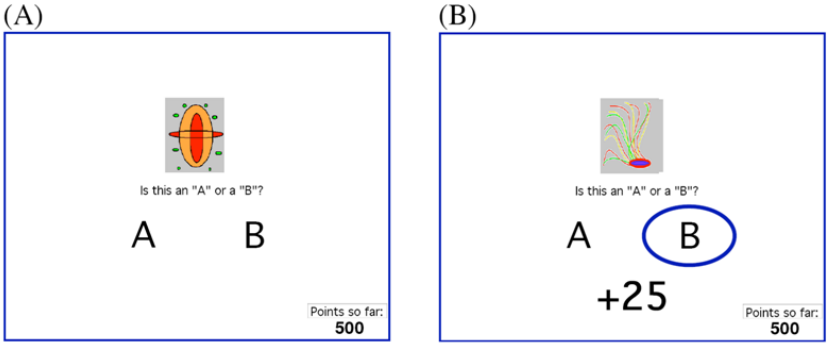


Table 4. Category and feedback structure of the probabilistic classification task

Stimulus	Probability Class A (%)	Probability Class B (%)	Feedback
S1	80	20	If correct: +25
S2	20	80	If incorrect: ø
S3	80	20	If correct: ø
S4	20	80	If incorrect: –25

The experiment was conducted on a Macintosh i-book, programmed in the SuperCard language. The participant was seated in a quiet testing room at a comfortable viewing distance from the screen. The keyboard was masked except for two keys, labelled “A” and “B” which the participant could use to enter responses. At the start of

the experiment, the participant read the following instructions: “In this experiment, you will be shown pictures, and you will guess whether those pictures belong to category “A” or category “B”. A picture does not always belong to the same category each time you see it. If you guess correctly, you may win points. If you guess wrong, you may lose points. You will see a running total of your points as you play. We will start you off with a few points now. Press the mouse button to begin practice.”

The practice phase then walked the participant through an example of a correct and an incorrect response to a sample trial in the punishment-learning task and an example of a correct and incorrect response to a sample trial in the reward- learning task. These examples used images other than those assigned to S1-S4. The participant saw a practice image, with a prompt to choose category A or B, and a running tally of points at the lower right corner of the screen. The tally is initialized to 500 points at the start of practice. The participant was first instructed to press the “A” key, which resulted in a punishment of –25 and updated point tally and then the “B” key, which resulted in no feedback. The participant then saw a second practice figure and was instructed first to press the “B” key which resulted in a reward of +25 and updated point tally and then the “A” key, which resulted in no feedback.

After these two practice trials, a summary of instructions appeared: “So… For some pictures, if you guess CORRECTLY, you WIN points (but, if you guess incorrectly, you win nothing). For other pictures, if you guess INCORRECTLY, you LOSE points (but, if you guess correctly, you lose nothing). Your job is to win all the points you can – and lose as few as you can. Remember that the same picture does not always belong to the same category. Press the mouse button to begin the experiment.” From here, the experiment began. On each trial, the participant saw one of the four stimuli (S1, S2, S3, S4) and was prompted to guess whether it was an “A” or a “B”. On trials in the reward-learning task (with stimuli S1 or S2), correct answers were rewarded with positive feedback and gain of 25 points; incorrect answers received no feedback. On trials in the punishment-learning task (with stimuli S3 or S4), incorrect answers were punished with negative feedback and loss of 25 points; correct answers received no feedback. The task contained 160 trials. Within a block, trial order was randomized. Trials were separated by a 2 second interval, during which time the screen was blank. Within each block, each stimulus appeared 10 times, 8 times with the more common

outcome (e.g. category “A” for S1 and S3 and “B” for S2 and S4) and 2 times with the less common outcome. Thus, training on the reward-learning task (S1 and S2) and punishment-learning task (S3 and S4) were intermixed. The no-feedback outcome, when it arrived, was ambiguous, as it could signal lack of reward (if received during a trial with S1 or S2) or lack of punishment (if received during a trial with S3 or S4). At the end of the 160 trials, if the participant’s running tally of points was less than 525 (i.e. no more than the points awarded at the start of the experiment), additional trials were added on which the participant’s response was always taken as correct, until the tally is at least 525. This was done in an attempt to minimize frustration in participants by ensuring that all participants terminated the experiment with more points than they had started with. Data from any such additional trials were not analyzed. On each trial, the computer recorded whether the participant made the optimal response (i.e. category A for S1 and S3, and category B for S2 and S4) regardless of actual outcome.

Personality measures

Following the probabilistic classification task, all participants were administered the Hungarian version of the TCI questionnaire, which has a good test-retest reliability (Rózsa et al. 2005). The TCI is suitable for the assessment of temperament and character traits. In this study, we focused on the temperament traits of novelty seeking (exploratory excitability, impulsiveness, extravagance, disorderliness), harm avoidance (anticipatory worry, fear of uncertainty, shyness, fatigability), and reward dependence (sentimentality, openness to warm communication, attachment, dependence), and persistence (eagerness of effort, work hardened, ambitious, perfectionist) (Cloninger, 1994). Thus, in addition to the main focus on novelty seeking and harm avoidance, data also were collected on reward dependence and persistence in order to test the specificity of possible alterations in personality traits.

Data analysis

The normality of data distribution was checked using Kolmogorov-Smirnov tests. All data were normally distributed ($p>0.1$). Analyses of variance (ANOVAs)

using the general linear model panel of the STATISTICA 7.0 software (StatSoft, Inc., Tulsa) were used to compare controls, never-medicated, and recently-medicated PD patients, and to compare the performance of patients at baseline (no medication) and at follow-up (dopamine agonists). ANOVAs were followed by planned *F* tests and Tukey Honestly Significant Difference (HSD) tests. Two-tailed *t* tests were used for the analysis of demographic data and personality measures. Pearson's product-moment correlation coefficients were calculated between test performance and personality measures. The Williams test was used to compare the correlation coefficients. The level of significance was set at alpha<0.05.

3.2.2. Tasks in the stimulus-learning experiment

Associative learning test

Stimuli were presented and responses were collected using a Macintosh Power-Book laptop. The antecedent stimuli were four drawings of faces (man, woman, girl, boy). The consequents were drawings of fish colored red, orange, purple, and pink. For each participant, stimuli were randomly assigned as antecedent and consequent stimuli. At the start of the experiment, the following instruction appeared on the screen: "Welcome to the experiment. You will see drawings of people who each have some pet fish. Different people have different kinds of fish. Your job is to learn which kinds of fish each person has. At first, you will have to guess." The experimenter read the instruction aloud to the participant and then clicked the mouse button to begin the acquisition phase. On each trial, a face and two fish drawings were displayed on the computer screen along with the prompt: "Which fish does this person have? Use the Left or Right key to choose". The participant responded with pressing one of two separate keys labeled as "LEFT" and "RIGHT" to indicate whether the fish on the left or the fish on the right was associated with the face. The selected fish drawing was circled and corrective feedback was given (***Figure 4***). In the case of an incorrect response, an alert beep sounded. The left-right ordering of the fish drawings was randomized across subjects. There were three stages in the acquisition phase (***Table 5***).

Stages 1 and 2 terminated after 8 consecutive correct responses, whereas stage 3 terminated after 12 consecutive correct responses. The participant was not informed on the beginning of a new stage. After the termination of the acquisition phase, a new instruction appeared on the screen, informing the participant that the task would remain the same but feedback would no longer be provided. The participant was not informed of the presence of new associations. The transfer phase consisted of 48 trials of which 12 trials were new associations for the testing of learned equivalence and 36 trials were old associations trained during the acquisition phase. The dependent measures were the mean number of errors in the acquisition phase and the proportion of incorrect responses in the transfer phase (for methodological details, see Myers et al., 2003).

After the computer-administered testing phase, participants received cards (size: 5 x 5 cm) depicting the faces and fishes. The task was to pair fishes and faces as learned during the test. The dependent measure was the percentage of correctly retrieved face-fish associations. After the card sorting test, participants were asked to read a newspaper article for 5-min. After this, the original computer-administered testing phase was repeated.

Figure 4. Example screen events during one trial. (A) Stimuli appear. (B) Participant responds and corrective feedback is given.

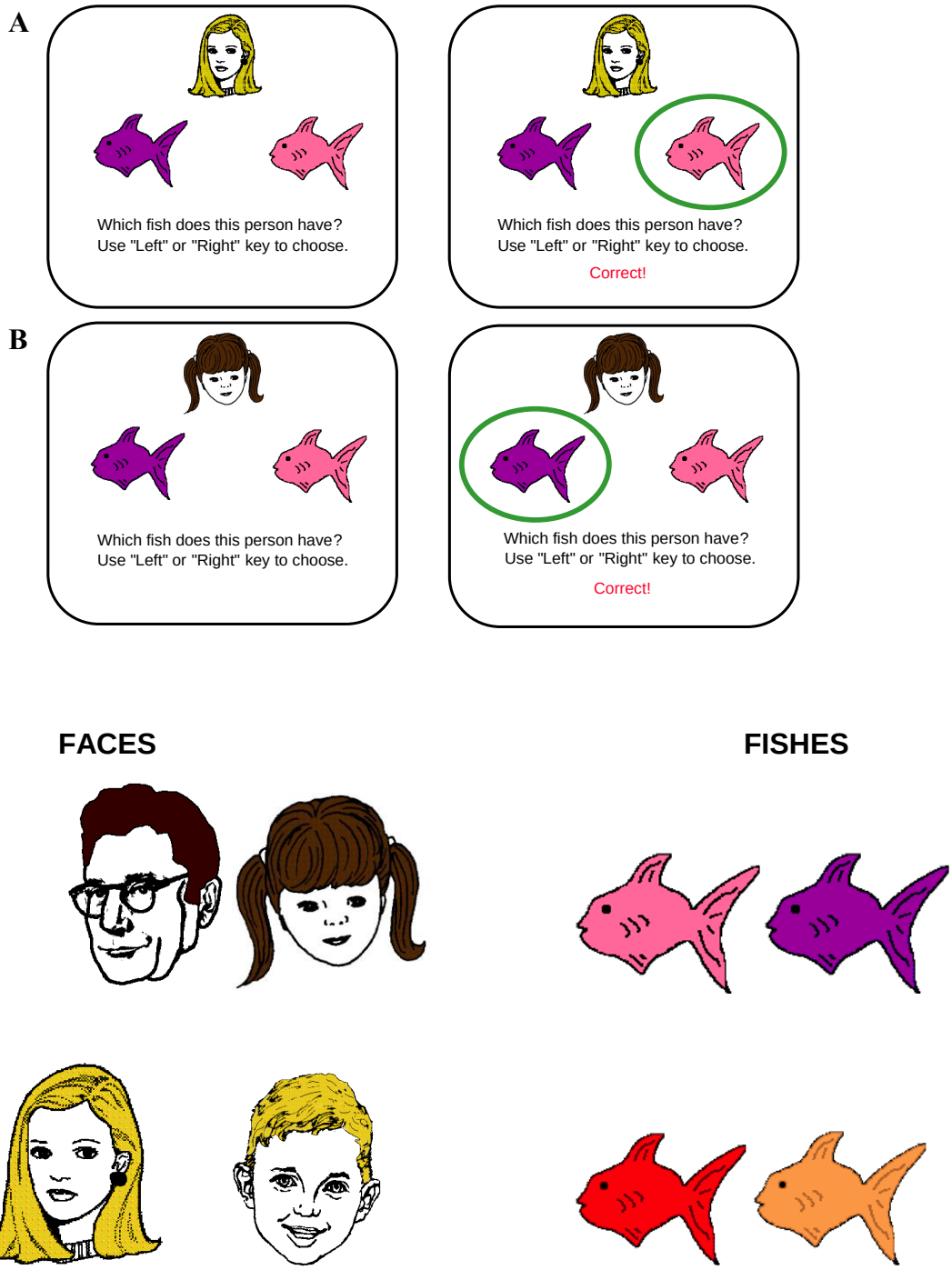


Table 5. Acquired equivalence learning

Acquisition Stage 1: Shaping	Acquisition Stage 2: Equivalence Training	Acquisition Stage 3: New Consequents	Transfer Phase: Equivalence Testing
A1 → X1	A1 → X1	A1 → X1	A2 → X2?
	A2 → X1	A2 → X1	
		A1 → X2	
B1 → Y1	B1 → Y1	B1 → Y1	B2 → Y2?
	B2 → Y1	B2 → Y1	
		B1 → Y2	

Data analysis

The number of errors in the training phase of the associative learning test and the clinical parameters were analyzed with two-tailed *t* tests and Mann-Whitney U test (this non-parametric analysis was used for MMSE values which showed non-Gaussian distribution). Errors from the testing phase were analyzed with a three-way repeated measures analysis of variance (ANOVA) which had the following design: 2 (group) by 2 (immediate vs. delayed testing) by 2 (old vs. new associations). A two-way ANOVA was used for the analysis of errors from the card pairing test with a 2 (group) by 2 (old vs. new associations) design. Tukey Honestly Significant Difference Test (HSD) was used for post hoc analysis. The level of significance was alpha<0.05.

3.2.3. **Tasks in the visuospatial assessment**

Clock drawing test

After receiving a pencil and a blank sheet of paper, participants were told, "I would like you to draw a clock, put in all the numbers, and set the hands for 10 after 11." The drawings were analyzed by two judges (WD and NB) who were blinded to the diagnosis and identity of each individual in our study.

The judges followed the quantitative (overall) scoring system, set out by Rouleau et al. (1992), with a maximum of 10 points. It was designed to examine the clock face (maximum, 2 points), layout of numbers (maximum, 4 points), and the position of the hands (maximum, 4 points). The average score of the raters was used in the analysis.

Qualitative error scoring was done according to six error types also employed by Rouleau et al.: (1) clock sizes that are either large (greater than 12.7 cm) or small (less than 3.81 cm); (2) graphic difficulties such as distortions in the clock face, hands or a general clumsy performance; (3) stimulus-bound responses that are either pure (also known as the "frontal pull" response), where the hands are set to 10 *to* 11 instead of 10 *after* 11; or other types of stimulus bound responses that are *also* rated as conceptual errors, such as the time written on the clock, absent hands or hands pointed to 10 or 11; (4) conceptual deficits that include misrepresentation of the time, such as the hands are absent or inadequately displayed; or misrepresentation of the clock face, such as a clock without numbers or the inappropriate use of numbers; (5) spatial or planning deficits that include neglect of the left half of the clock, gaps between numbers, numbers outside the clock, and counterclockwise layout of numbers; and (6) perseveration of hands or numbers. A qualitative error was considered present only if both judges agreed on its presence.

The judges reviewed each clock independently and in a random order. Using a two-way random effects model based on consistency, the interrater reliability intraclass correlation coefficient of the average rater for overall scores was .95 (.92–.96), $p < .001$. Cohen's kappa measure of agreement between the raters on qualitative measures ranged

from fair to excellent (.49–.8). The Cohen's kappa value and standard error for qualitative measures were as follows: clock size (.54 ± .12), graphic difficulty (.49 ± .1), stimulus-bound responses (.73 ± .08), conceptual deficits (.66 ± .08), spatial or planning deficits (.59 ± .09), and perseveration (.8 ± .11).

All participants were administered the DRS-2 except for 4/36 FTD and 5/25 AD patients, whereas all received the MMSE. Time pressure during clinic visits resulted in the missing DRS-2 data.

Data analyses

A multivariate analysis of variance (MANOVA) was conducted to assess age, education, MMSE, and DRS-2 scores among the groups. Tukey-Kramer *post hoc* comparisons were done. A *t* test was performed to examine duration of illness differences between the dementia groups. Gender differences among the groups were analyzed using the chisquare test. An analysis of covariance (ANCOVA) was performed to examine overall CDT scores among the control, FTD, and AD groups using age and education as covariates. *Post hoc* tests were conducted with a Bonferroni adjustment. Chi-square tests were performed to analyze qualitative error frequencies among the groups. Alogistic regression analysis was utilized to discriminate AD patients from the FTD group based on CDT measures. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 10.1 for Windows, Chicago, IL, USA) and all hypotheses were tested at alpha level of .05 (2-tailed).

4. RESULTS

4.1. Results in the reinforcement learning experiment

4.1.1. Differences between never-medicated and recently-medicated PD patients in sensitivity to positive and negative feedback

The results from the feedback-based task are shown in ***Figure 5***. The ANOVA, in which group (controls, never-medicated and recently-medicated PD patients) was the between-subject factor and feedback-type (positive and negative) and trial blocks were the within-subject factors, revealed significant main effects of group ($F(2,65)=10.76$, $p<0.001$) and trial blocks ($F(3,195)=91.40$, $p<0.001$). The two-way interaction between group and feedback-type was significant ($F(2,65)=210.11$, $p<0.001$), as was the three-way interaction among group, feedback-type, and trial blocks ($F(6,195)=22.84$, $p<0.001$). The main effect of feedback-type ($F(1,65)=0.45$, $p=0.5$), the interaction between feedback-type and trial blocks ($F(3,195)=2.06$, $p=0.1$), and the interaction between group by trial blocks ($F(6,195)=1.82$, $p=0.1$) did not reach the level of significance.

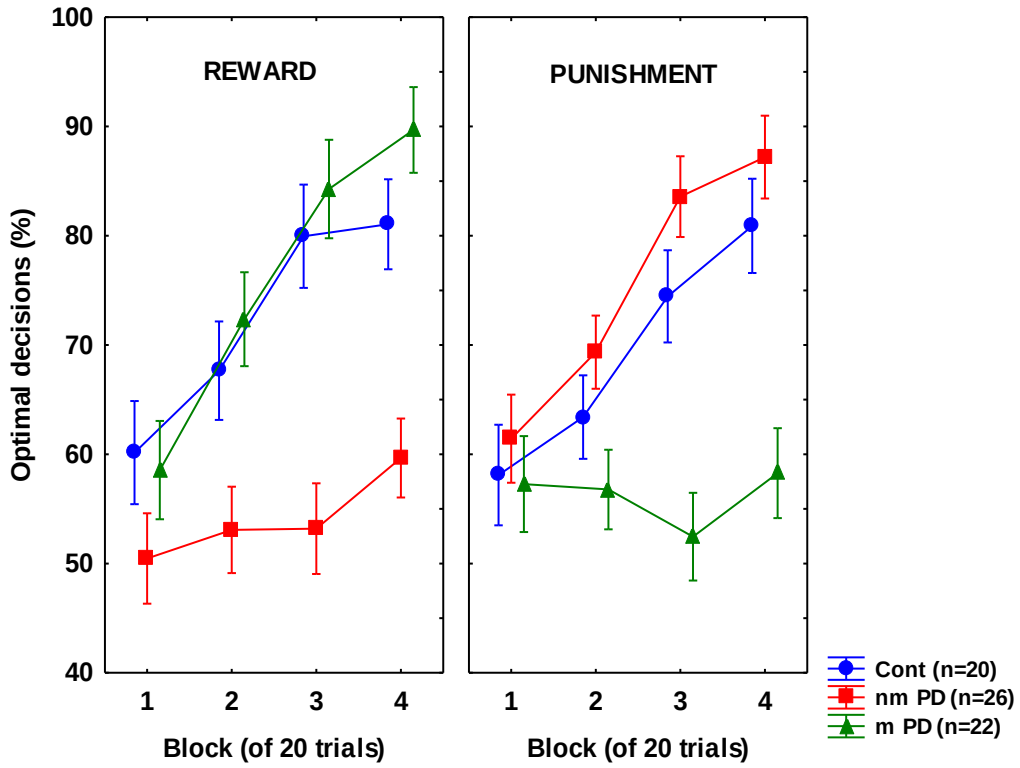
This three-way interaction was further investigated by *F* tests for linear trend. First, the controls were compared with the never-medicated PD patients. This analysis revealed a significant interaction among group, feedback-type, and trial blocks ($F(1,65)=10.53$, $p<0.001$). Second, the controls were compared with the recently-medicated PD patients. This analysis also revealed a three-way interaction ($F(1,65)=34.14$, $p<0.001$). Finally, a similar interaction was observed when the never-medicated and the recently-medicated patients were compared ($F(1,65)=91.45$, $p<0.001$).

Tukey HSD tests conducted on the group-by-feedback-type interactions revealed that the never-medicated PD patients displayed significantly impaired performance on reward learning as compared with the controls ($p<0.001$), whereas the opposite effect was found for punishment learning: the patients outperformed the controls ($p<0.01$) (***Figure 5***). When the recently-medicated PD patients were compared with the controls, there was no significant difference for reward learning ($p=0.19$), but the patients

displayed significantly impaired performance on punishment learning ($p<0.001$) (***Figure 5***). Finally, when the recently-medicated and the never-medicated PD patients were compared, we found that the recently-medicated group outperformed the never-medicated group in the reward condition ($p<0.001$), whereas the opposite was found in the punishment condition ($p<0.001$) (***Figure 5***).

These differences were not due to confounding variables such as age, education, IQ, or socioeconomic status, because the patient groups and controls were similar in these measures. In addition, the above described analyses remained the same when time since diagnosis and UPDRS scores were included as co-variants (time since diagnosis was significantly different between never-medicated and recently-medicated patients, whereas UPDRS scores were not) (***Table 1***, *see participants*).

Figure 5. Results from the feedback-based probabilistic classification task. The never-medicated Parkinson's patients (nmed PD) outperformed the recently-medicated patients (med PD) in the punishment condition, whereas the recently-medicated patients outperformed the never-medicated patients in the reward condition ($p<0.001$). Data are mean, error bars indicate standard errors.



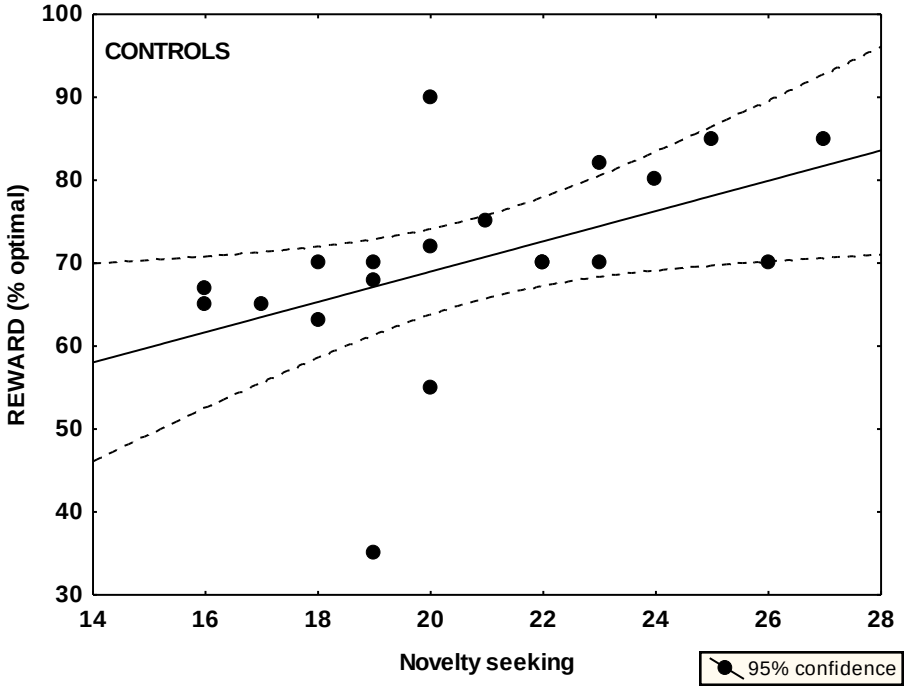
4.1.2. Personality measures in never-medicated and recently-medicated PD patients

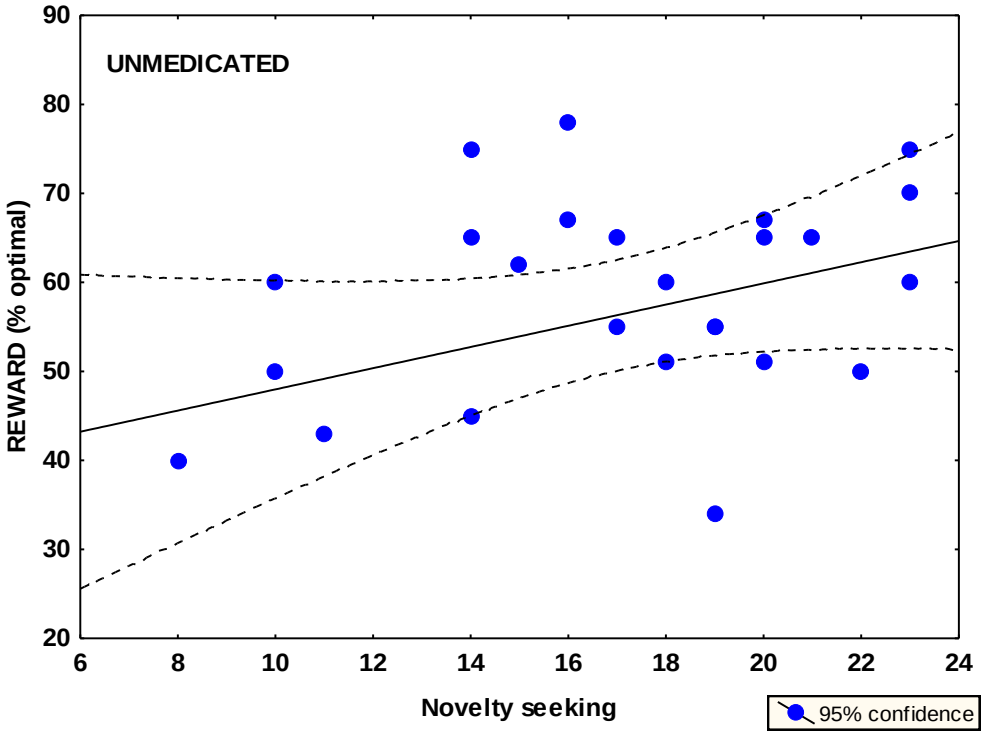
Data from the TCI are shown (***Table 1***, *see participants*). One-way ANOVAs indicated a significant main effect of group only in the case of novelty seeking ($F(2,65)=13.72$, $p<0.0001$). The never-medicated PD patients exhibited significantly lower novelty seeking scores compared with controls ($t(44)=3.34$, $p<0.005$) and with recently-medicated patients ($t(46)=-4.66$, $p<0.0001$). In addition, the recently-medicated patients exhibited significantly higher novelty seeking scores compared with the controls ($t(40)=-2.34$, $p<0.05$).

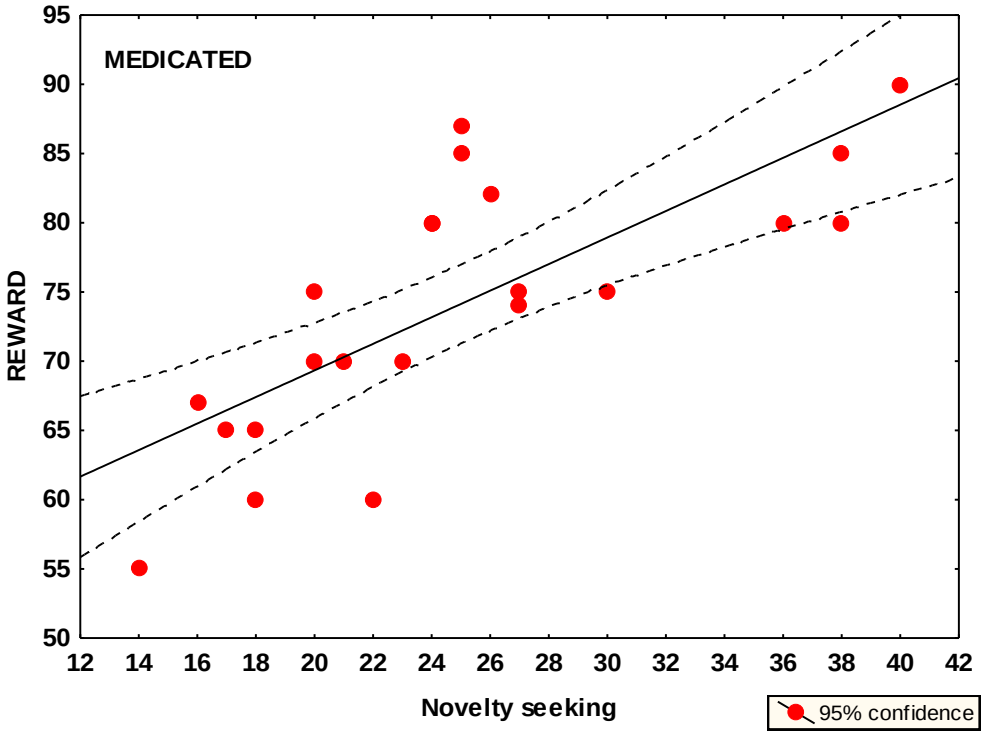
4.1.3. Correlation between performance on the feedback-based task and personality measures

In the healthy control group, there was a significant positive relationship between the percent of optimal choices on the feedback-based task for positive feedback (reward) and novelty seeking scores ($r=0.49$, $p<0.05$). A similar tendency was observed in never-medicated PD patients, but this did not reach the level of statistical significance ($r=0.31$, $p>0.1$). Finally, we observed the strongest positive correlation in recently-medicated PD patients ($r=0.75$, $p<0.001$) (***Figure 6***). The correlation coefficients from the never-medicated and the recently-medicated group showed a significant difference (Williams test, $p<0.05$).

Figure 6. Correlations between novelty seeking and reward learning in controls (black), never-medicated Parkinson's patients (blue), and recently-medicated patients (red)





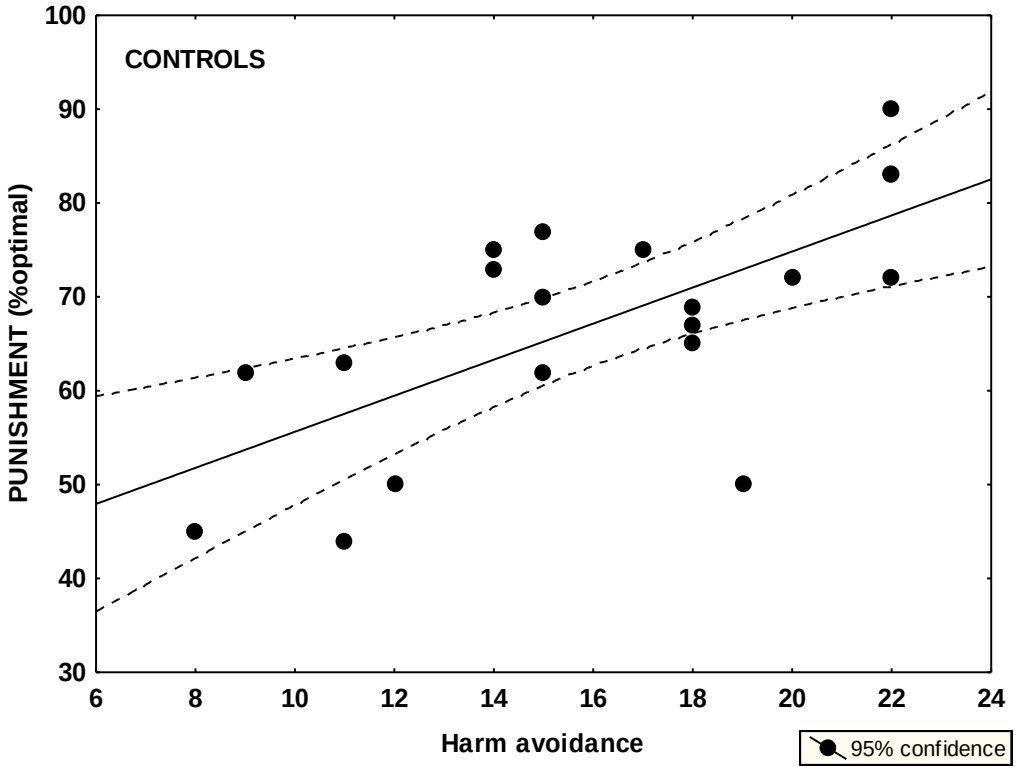


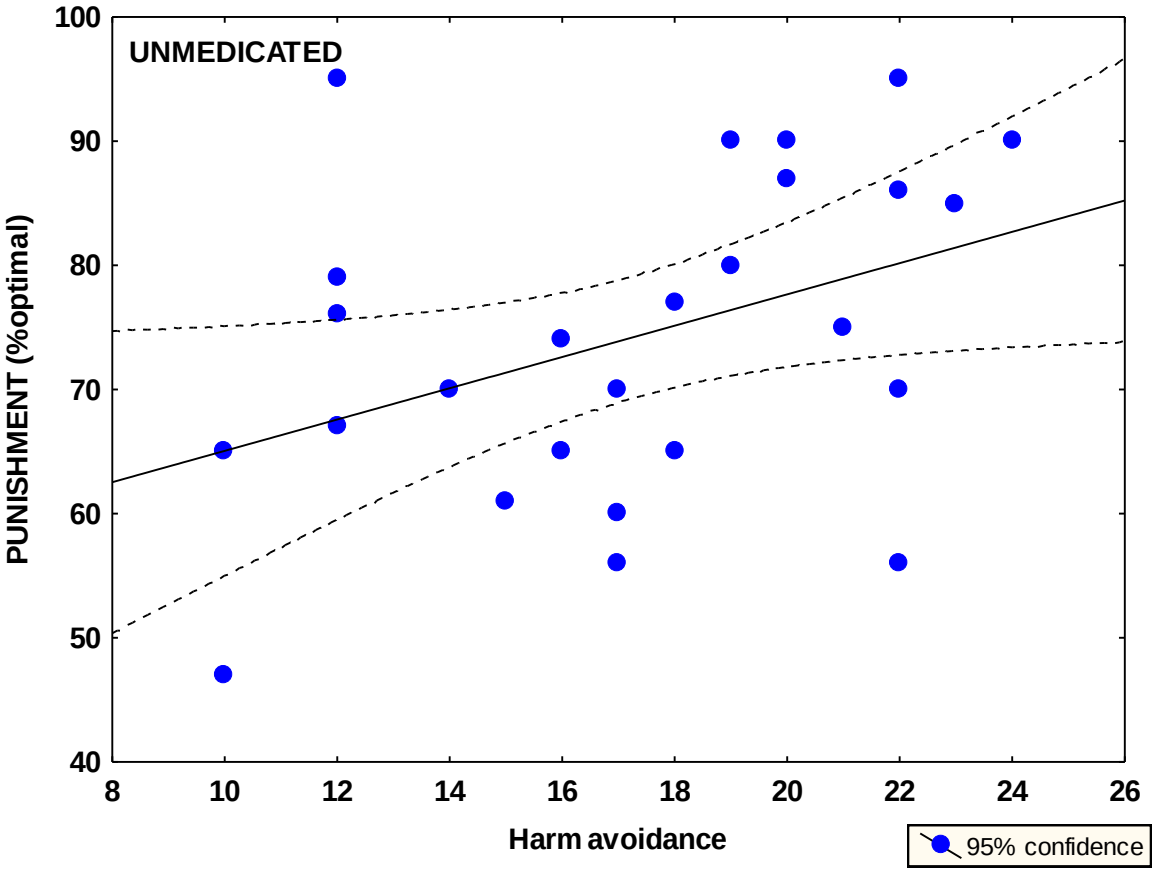
In the healthy control group, we also observed a significant positive correlation between the percent of optimal choices on the feedback-based task for negative feedback (punishment) and harm avoidance scores ($r=0.67$, $p<0.01$), which also was

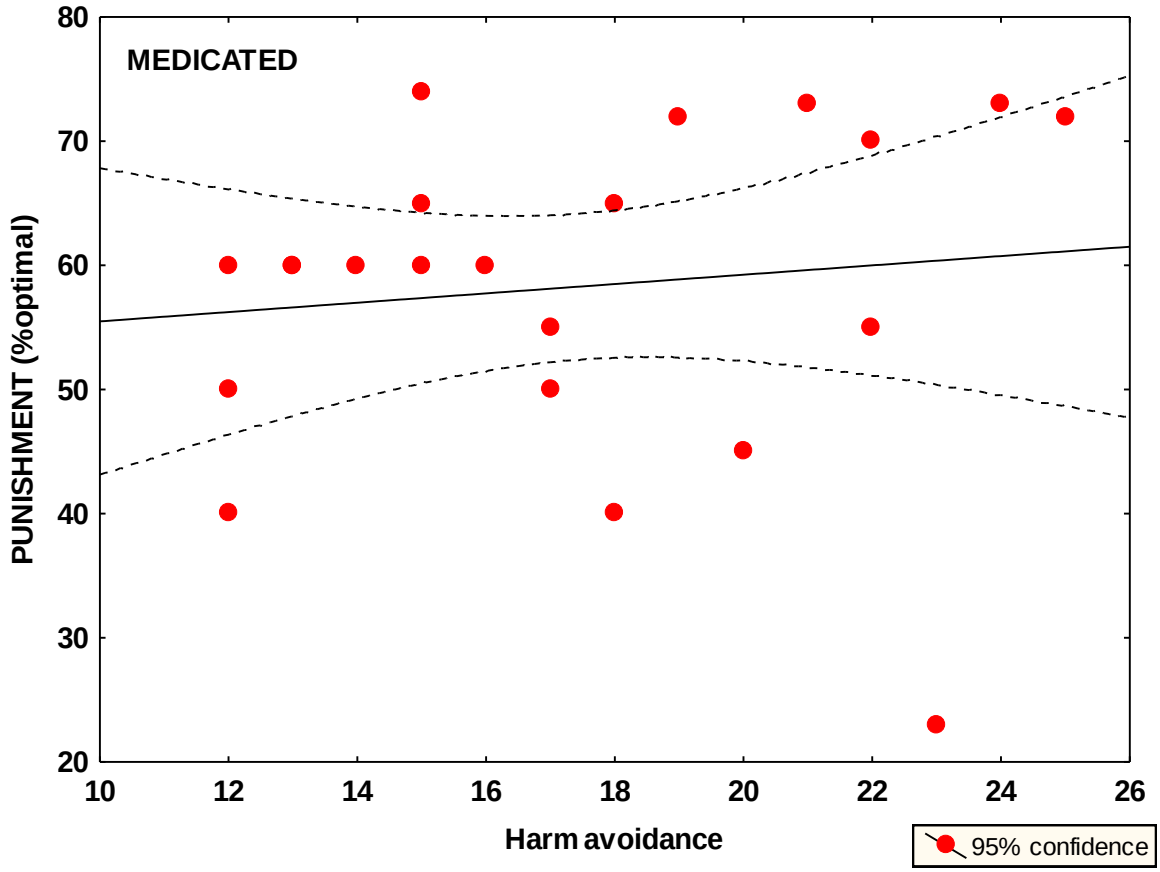
present in never-medicated PD patients ($r=0.40$, $p<0.05$) but not in recently-medicated patients ($r=0.11$, $p>0.1$) (***Figure 7***). The correlation coefficients from the controls and the recently-medicated group showed a significant difference (Williams test, $p<0.05$).

When the correlation analysis was corrected for multiple comparisons (Bonferroni, alpha adjusted to 0.002), only the correlation between novelty seeking and reward learning in the recently-medicated PD group, and the correlation between harm avoidance and punishment learning in the controls reached the level of significance.

Figure 7. Correlations between harm avoidance and punishment learning in controls (black), never-medicated Parkinson's patients (blue), and recently-medicated patients (red)




UNMEDICATED
PUNISHMENT (%optimal)
100
90
80
70
60
50
40
8
10
12
14
16
18
20
22
24
26
Harm avoidance
95% confidence



4.1.4. **Longitudinal result from the feedback-based task: retesting the never-medicated PD patients after the initialization of dopamine agonist therapy**

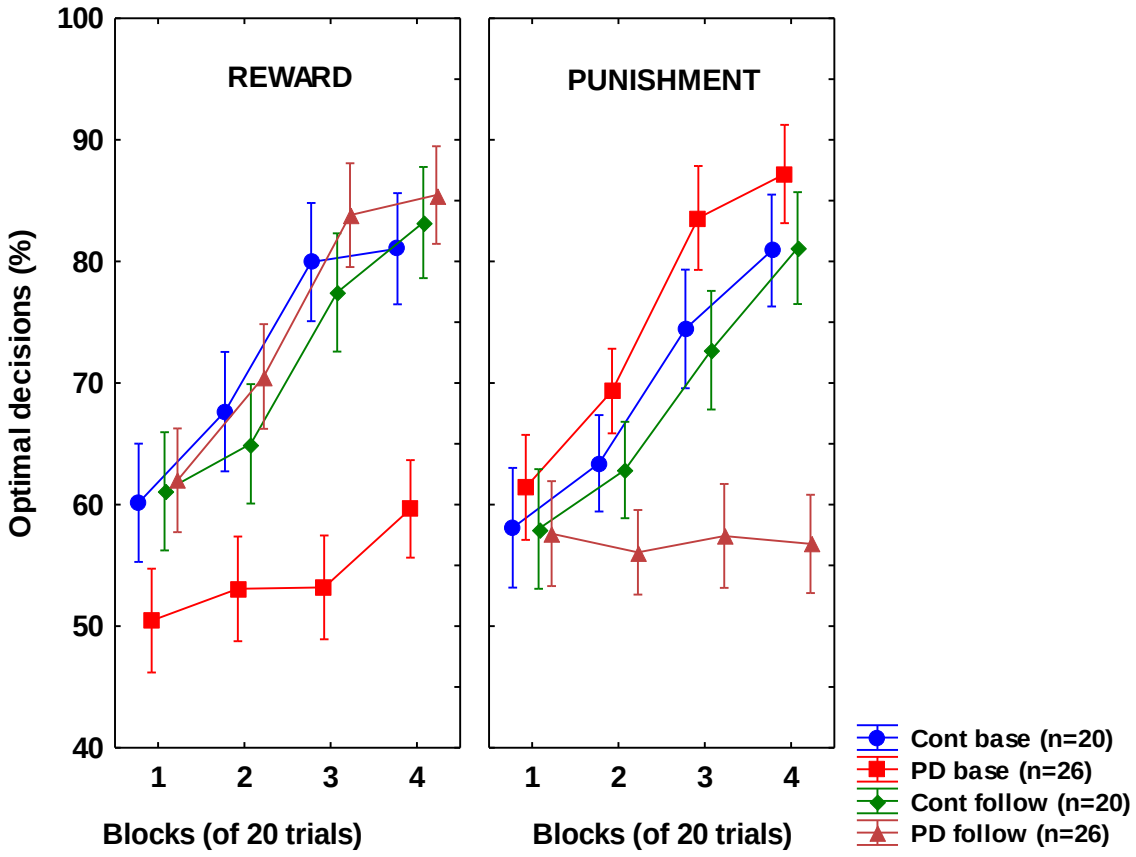
At the follow-up phase, the mean UPDRS score was 26.4 (SD=6.4), which was significantly lower than the score at baseline testing (mean: 30.8, SD=6.4, $t(48)=2.43$, $p<0.05$). The HAM-D (mean at follow-up: 4.1, SD=2.1) and HAM-A (mean at follow-up: 3.2, SD=1.8) scores did not change relative to the baseline.

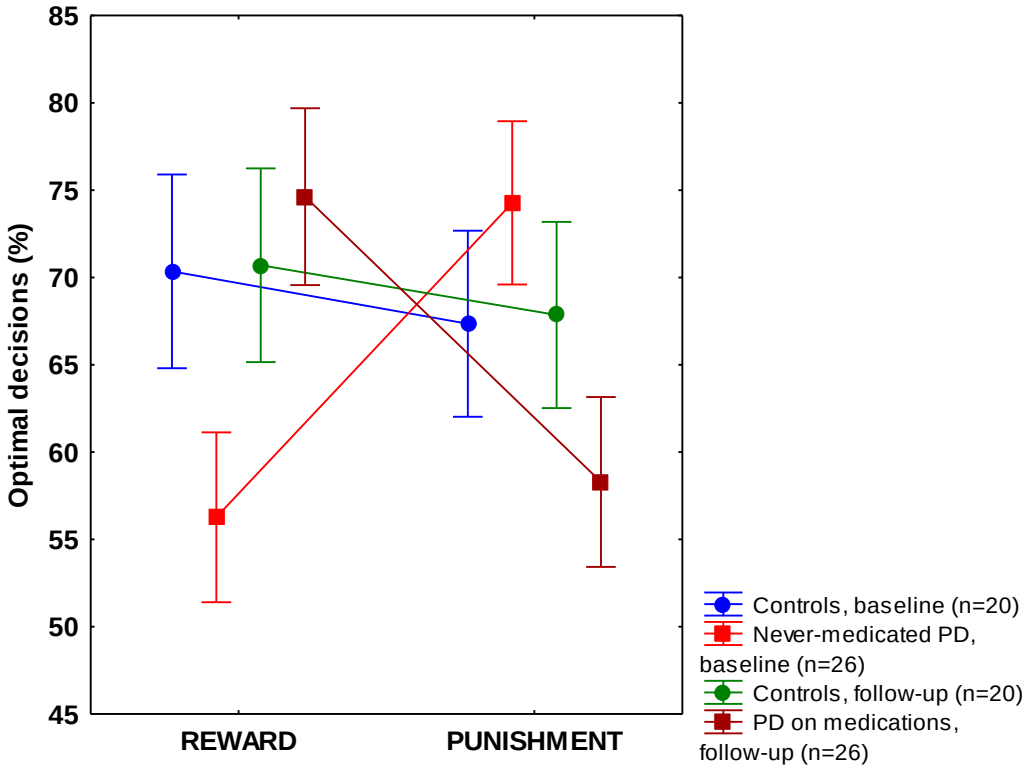
The longitudinal results from the feedback-based task are shown in ***Figure 8***. We tested how medication affected feedback-based task performance in patients with PD using an ANOVA_in which group (controls vs. PD) was the between-subject factor and testing time (baseline vs. follow-up), feedback-type (positive vs. negative), and trial blocks were the within-subject factors. This analysis revealed significant main effects of group ($F(1,44)=13.47$, $p<0.01$) and trial blocks ($F(3,132)=58.08$, $p<0.001$)._The main effects of testing time ($F(1,44)=2.04$, $p=0.2$) and feedback-type ($F(1,44)=0.98$, $p=0.3$) were not significant. There were significant two-way interactions between group and testing time ($F(1,44)=15.42$, $p<0.001$), group and feedback-type ($F(1,44)=4.46$, $p<0.05$),

group and trial blocks ($F(3,132)=2.75$, $p=0.05$), and testing time and feedback-type ($F(1,44)=149.18$, $p<0.001$). The two-way interactions between testing time and trial blocks ($F(3,132)=0.41$, $p=0.7$) and feedback and trial blocks ($F(3,132)=1.52$, $p=0.2$) were not significant. The three-way interactions among group, testing time, and feedback-type ($F(1,44)=148.62$, $p<0.001$) and group, testing type, and trial blocks ($F(3,132)=3.77$, $p<0.05$) were significant, whereas the interaction among group, testing time, and trial blocks ($F(3,132)=1.24$, $p=0.3$) was not significant. Finally, the four-way interaction among group, testing time, feedback-type, and trial blocks was significant ($F(3,132)=14.21$, $p<0.001$). The four-way interaction was examined by an *F* test for linear trend, which confirmed the interaction ($F(1,44)=29.08$, $p<0.001$).

These complex results were further analyzed using Tukey HSD tests, which were conducted on the critical group by testing time by feedback-type interaction. As an important control condition, these tests indicated that the performance of the controls was similar at baseline and follow-up for both reward and punishment ($p>0.5$). Critically, in patients with PD, there were significant differences between the baseline and follow-up results: dopaminergic medications robustly improved reward learning ($p<0.001$) and disrupted punishment learning ($p<0.001$) (***Figure 8***). At the follow-up assessment, the PD patients did not differ from controls on reward learning ($p=0.12$), whereas they performed less effectively than controls on punishment learning ($p<0.001$).

Figure 8. Results from the feedback-based probabilistic classification task at baseline and at follow-up when Parkinson's patients (PD) received pramipexole and ropinirole. In reward learning, performance in the unmedicated baseline condition (base) was significantly worse than in the medicated follow-up condition (follow), whereas in punishment learning, performance in the unmedicated condition was significantly better than in the medicated condition ($p<0.001$). Data are mean, error bars indicate standard errors.





4.1.5. Longitudinal data from personality measures

Dopaminergic medications significantly increased novelty seeking (mean at follow-up: 20.3, SD=6.2, $t(48)=-2.26$, $p<0.05$), whereas harm avoidance (mean at follow-up: 14.9, SD=3.2) and reward dependence (mean at follow-up: 16.0, SD=4.2) did not change significantly ($p>0.1$). This was not accompanied by clinical changes in mood and anxiety, because HAM-D and HAM-A scores were similar at the baseline and at the follow-up assessment.

4.1.6. Effect of different dopamine agonists, illness duration, and symptoms

Data from the feedback-based task and TCI did not differ between patients receiving pramipexole and ropinirole ($F<2$, $p>0.1$). There were no significant correlations between the primary measures (performance on the feedback-based task and TCI scores), illness duration, and UPDRS/HAM-A/HAM-D scores (all $p>0.1$).

4.2.Results in the stimulus-learning experiment

4.2.1. Training phase

Twenty-two AD patients out of the original sample of 25 patients were able to complete the training phase. Patients with AD committed more errors (mean: 14.8, SD=7.0) compared with controls (mean: 8.5, SD=3.6), $t(40)=-3.64$, $p<0.01$.

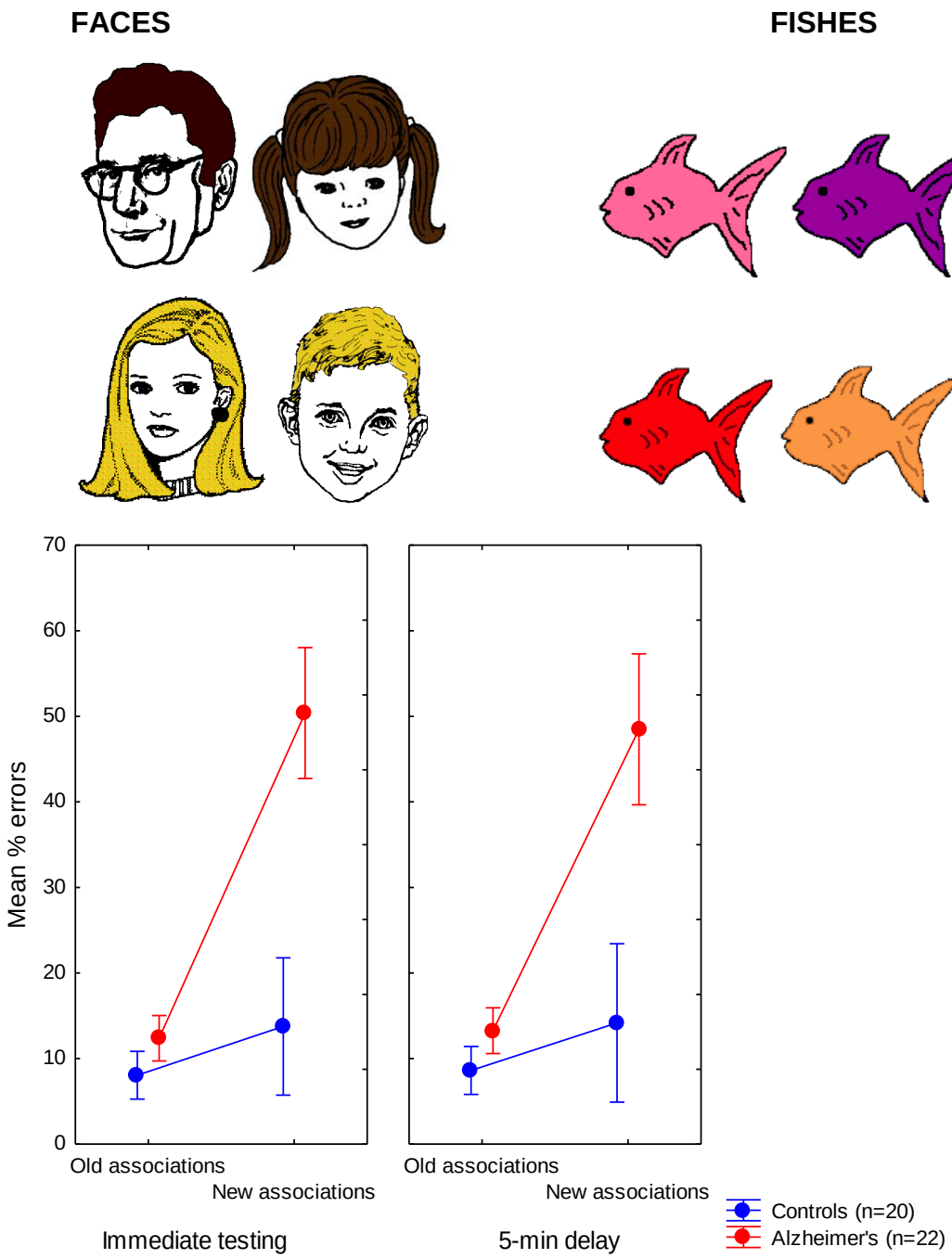
4.2.2. Transfer phase

The ANOVA indicated significant main effects of group, $F(1,40)=40.76$, $p<0.0001$, and type of associations (old vs. new), $F(1,40)=61.60$, $p<0.0001$. There was a significant interaction between group and type of associations, $F(1,40)=33.16$, $p<0.0001$. All other main effects and interactions, including the delay phase, were not significant, $F<1$, $p>0.5$. Tukey HSD tests revealed that patients with AD were severely impaired in the case of new associations (acquired equivalence) ($p<0.001$) but not in the case of old associations, $p>0.5$ (***Figure 9***).

4.2.3. Card pairing test

The ANOVA indicated significant main effects of group, $F(1,40)=40.76$, $p<0.0001$, and type of association, $F(1,40)=61.6$, $p<0.0001$. The two-way interaction between group and type of association was also significant, $F(1,40)=33.16$, $p<0.0001$. Tukey HSD tests revealed that patients with AD showed lower performance than controls in the case of old and new associations ($p<0.001$).

Figure 9. Performance in the transfer phase of the task (immediate and delayed testing). Old associations refer to fish-face pairs exposed in the training phase. New associations refer to never trained pairs learned during acquired equivalence. Error bars indicate 95% confidence intervals.



4.3.Results in the visuospatial assessment

4.3.1. Demographic and cognitive test results for groups

Table 3 (*see participants*) shows demographic characteristics and cognitive test results of the groups.A MANOVA showed a significant difference between the groups in demographic variables [Pillai's Trace=1.03, $F(8,146)=19.41$, $p < .001$]. Age was significantly different among the groups, $F(2,75)=33.72$, $p < .001$. On Tukey-Kramer *post hoc* analysis, the AD group was significantly older than the FTD, $p < .001$, and control groups, $p < .001$. No difference in age was found between the control and FTD groups, $p = .92$. There were no significant differences among the groups in education, $F(2,75) = 1.82$, p .17. MMSE scores were significantly different among the groups, $F(2,75)= 34.76$, $p < .001$. On Tukey-Kramer *post hoc* analysis, the control group had significantly higher MMSE scores compared to the FTD, $p < .001$, and AD groups, $p < .001$. The FTD group had significantly higher MMSE scores than the AD group, $p = .04$. DRS-2 scores were significantly different among the groups, $F(2,75) = 27.46$, $p < .001$, with higher scores in the control group compared to the FTD, $p < .001$, and AD groups, $p < .001$, on Tukey-Kramer *post hoc* analysis. There was no significant difference in total DRS-2 scores between the dementia groups, $p = 1$. An independent samples *t* test showed that the time from onset of illness to testing (represented as duration of illness in ***Table 3***, *see participants*) was similar between the dementia groups, $t(58)= .77$, $p=.45$. Chi-square analysis showed no significant gender differences among the groups, $x^2(2, N= 86) =.86$, $p =.65$.

4.3.2. Overall and error analysis of CDT comparing control, AD, and FTD groups

Figure 10 shows the quantitative CDT scores for the groups. An ANCOVA covarying for age and education showed a significant difference in overall scores among the groups, $F(2,80)=19.97$, $p < .001$ (see ***Table 3***). *Post hoc* analysis with a Bonferroni adjustment showed that the control group had significantly higher scores than the FTD, $p < .001$, and AD groups, $p < .001$. The adjusted means for the control, FTD, and AD groups were 9.6 (SE=5.38), 7.62 (SE=5.33), and 5.53 (SE= 5 .48), respectively. The FTD group had significantly higher scores than the AD group, $p < .01$. A second

ANCOVA comparing the dementia groups covarying for severity of dementia as measured by the MMSE in addition to age and education still showed significantly higher overall scores in the FTD group compared to the AD patients, $p < .047$.

Figure 10. Mean and individual data points of quantitative scores among the FTD (*n* =36), AD (*n* =25), and control (*n* =25) groups.

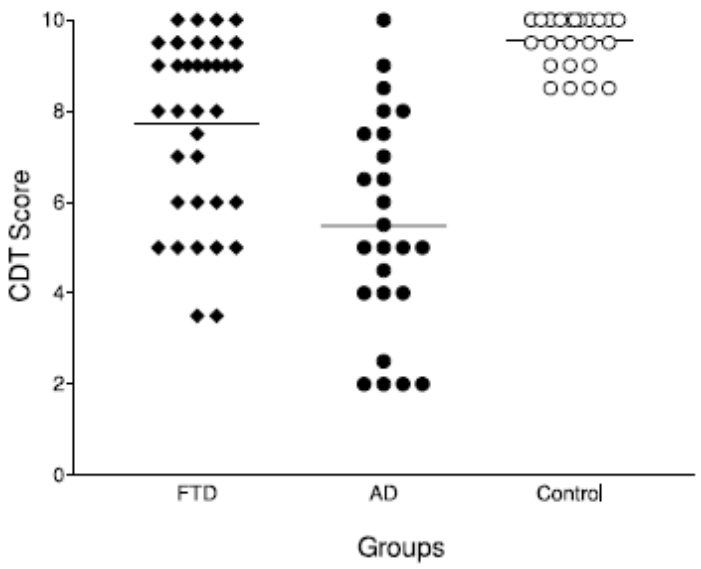
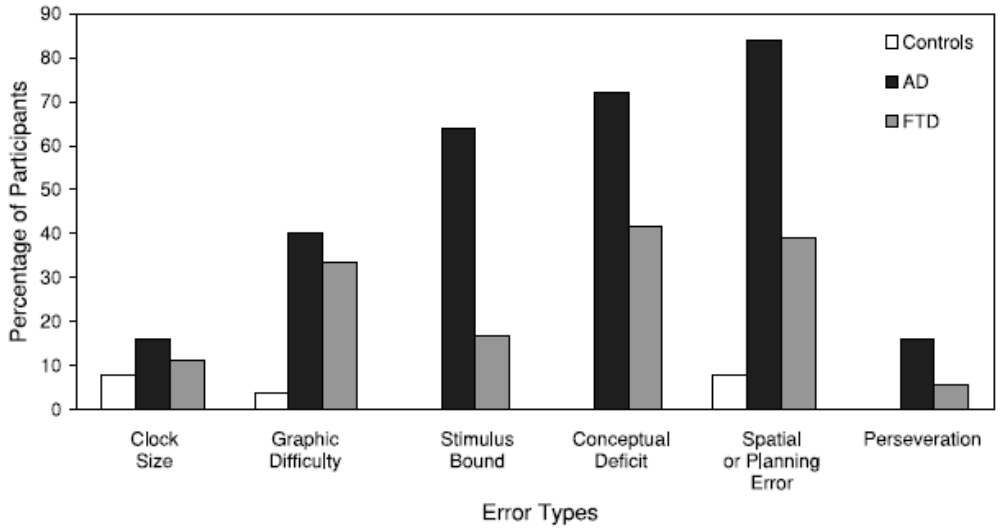


Figure 11 shows the percentage of different errors types committed by the groups. On qualitative error analysis using the chi-square test, the groups differed significantly in graphic, $x^2(2, N = 86) = 9.64$, $p < .01$, stimulus bound,$x^2(2,N.= 86) = 29.48$, $p < .001$, conceptual, $x^2(2, N = 86)=27.69$, $p < .001$, and spatial or planning errors, $x^2(2, N= 86)= 29.89$, $p<.001$. Comparisons between the dementia groups showed significantly fewer errors in stimulus bound responses, $p < .001$, conceptual deficits, $p = .02$, and spatial or planning errors, $p < .001$, in FTD patients compared to the AD group. Subanalysis of stimulus-bound responses showed significantly fewer errors in the FTD group compared to the AD group in "frontal pull", $p = .04$, and stimulus bound responses that are also rated as conceptual errors, $p < .01$. Subanalysis of conceptual errors showed significantly fewer errors in misrepresentation of time, $p=.02$, in FTD patients compared to the AD group. No difference in misrepresentation of clock face was found between the groups, $p=.34$. Subanalysis of spatial or planning errors showed significantly more errors in the spatial layout of numbers, $p < .01$, and numbers outside the clock, $p = .03$, in AD patients compared to the FTD group. There was no difference between the groups in neglect of the left hemisphere, gaps before 12, 3, 6, and 9, and numbers arranged counter-clockwise, $p > .05$.

Figure 11. Percentage of control individuals (*n*=25) and FTD (*n*=36) and AD (*n*=25) patients making different kinds of qualitative errors.



The control group made significantly less errors in graphic difficulty, $p < .05$, fewer stimulus-bound responses, $p < .05$, conceptual deficits, $p < .05$, and spatial or planning errors compared to both FTD and AD patients. The AD group also made more perseverative errors compared to the control group, $p = .04$.

A logistic regression analysis was performed to discriminate AD patients from the FTD group. The analysis was done with a diagnosis of FTD or AD as the categorical dependent variable and overall scores, stimulus-bound responses, conceptual deficits, and spatial or planning errors as predictor variables. The model was significant, $x^2(4, N = 61) = 26.18$, $p < .001$, accounting for between 34.9% and 47% of the variance in discriminating FTD from AD patients. The model correctly classified 88.9% of FTD patients and 76% of AD patients with an overall prediction accuracy of 83.6%.

5. DISCUSSION

5.1. Outline of the results

The results of the present studies can be summarized as follows:

1. *Reward and punishment learning in PD.* Drug-free PD patients showed selective deficit on reward learning, whereas punishment learning was spared. After the administration of dopamine agonists, this pattern of performance was reversed: reward learning was improved, whereas punishment learning was disrupted. These findings were confirmed in a cross-sectional design (comparing medicated and unmedicated patients) and in a longitudinal design (comparing patients before and after medication).

2. *Personality traits in PD.* Drug-free PD patients showed lower novelty seeking than healthy controls. Dopamine agonists increased these scores. Novelty seeking and reward learning were positively correlated, and a similar relationship was found regarding punishment learning and harm avoidance. The other personality traits, as measured by the TCI, displayed less consistent relationships with learning and medication.

3. *Flexibility and generalization of stimulus-response associations in AD.* Patients with early AD were able to learn stimulus-response associations using trial-by-trial feedback following decisions. Generalization of these associations, as measured by acquired equivalence, was impaired. Moreover, when stimulus-response associations must be used in a situation requiring flexible declarative knowledge, AD patients were impaired, too.

4. *Visuospatial abilities in AD and FTD.* On the CDT FTD patients achieved significantly higher scores than the AD group. FTD patients were better in stimulus-bound responses, conceptual deficits, and spatial or planning errors. Overall, both quantitative and qualitative analyses of CDT differentiated between AD and FTD at the group level.

5.2. Reinforcement learning in PD

5.2.1. The role of dopamine in salience, motivation, and reward

Our results from PD patients suggest that dopamine is essential in reward signals: in the case of mesencephalic-striatal dopamine loss, reward learning is impaired but punishment learning is spared, and dopamine agonists reverse this pattern of deficit. Therefore, dopaminergic signals do not encode the general behavioral relevance of outcome signals (salience) regardless of their value (reward vs. punishment), as suggested by some authors (Berridge, 2007). However, one important issue must be mentioned: the drugs used in our study were agonists of the D2 and D3 dopamine receptors, and therefore it is not equivalent with a general increase of dopamine level or phasic dopamine release stimulating all receptor types. Second, it is unknown how these drugs affect reward learning in healthy persons and how they interfere with the altered dopaminergic status in PD. Third, dopaminergic neurotransmission was not directly visualized in our PD patients, and hence we have no direct data regarding dopamine loss in different subregions of the striatum or neuronal signals in these regions.

Frank and O'Reilly (2006) compared the effect of low doses of D2 agents cabergoline and haloperidol on reward and punishment learning in healthy volunteers. Paradoxically, cabergoline impaired, while haloperidol enhanced learning from positive reinforcement, which can be explained by their effect on the presynaptic autoreceptors in the low dose range. Cabergoline also caused a globally decreased inhibitory signal. Importantly, these effects were observed in the case of attention and working memory, suggesting that basal ganglia dopaminergic transmission contributes to the updating of prefrontal representations.

In addition to behavioral tasks, Pessiglione et al. (2006) used pharmacological functional neuroimaging to visualize the role of dopaminergic modulation in reward prediction error in humans. During learning, the magnitude of reward prediction error neuronal signal in the striatum was increased by L-dopa and decreased by haloperidol, a D2/D1 receptor antagonist. At the behavioral level, participants receiving L-dopa tended to chose the most rewarding action in contrast to participants on haloperidol. Antipsychotics with strong dopamine receptor antagonist properties dampen reward prediction signal in the ventral striatum (Juckel et al., 2006).

In contrast, Jensen et al. (2007) arrived at a different conclusion. These authors stressed that reward prediction studies focus on the role of ventral striatum in positive reinforcers, but it is not clear whether this region responds to behaviorally relevant aversive stimuli (e.g., a loud noise). Using functional neuroimaging, Jensen et al. (2007) showed that prediction error signal in the ventral striatum was not modulated by the valence of the stimuli (reward vs. punishment), in contrast to the orbitofrontal and insular regions that differentiated between reinforcers with positive and negative values. However, the clear relevance of these results regarding our data is not clear, given that Jensen et al. (2007) used a classic Pavlovian paradigm.

Au et al. (2011) used a set-shifting task to evaluate the effect of dopaminergic status on learning in PD. The response times was prolonged in PD patients when they received no L-dopa, which normalized it in the case of positive feedback (reward). The ability to set-shift using negative feedback was not affected in PD. Interestingly, positive feedback deactivated the lateral prefrontal cortex in unmedicated PD patients, whereas negative feedback enhanced brain activation in posterior sensorimotor regions. L-dopa ameliorated activation in the cortico-striatal loops but not in each region of the neocortex. In conclusion, PD patients' ability on the set-shifting task was modified by dopamine status and feedback valence. The key finding was the same as in our study: unmedicated PD patients had deficits when positive feedback was used, which was restored by dopamine replacement therapy.

Recent animal studies seem to detangle the components of general motivational and reinforcing signals. First of all, it seems that the mesocortical and mesolimbic dopaminergic pathways are involved in multiple functions, including hedonic impact of stimuli ("liking"), motivation ("wanting"), and prediction errors during associative learning ("correcting") (Smith et al., 2011). In a Pavlovian paradigm, rats were trained to associate stimuli with sucrose reward. If an opioid-stimulating drug was injected into the ventral striatum (nucleus accumbens), hedonic "liking" impact of sucrose was increased in parallel with the firing rates of neurons in the ventral pallidum. The incentive salience of stimuli was also encoded by these neurons but only if the stimuli were close to reward in time. In contrast, dopamine agonists enhanced the motivation component but did not affect hedonic aspects. There were different neuronal groups that encoded hedonic impact and incentive salience, and even these neurons' firing rate was

different for these functions (Smith et al., 2011). Separate striatal neuronal groups also exist for motor control, motivation, and reward prediction (Ena et al., 2011).

Direct registrations from dopaminergic neurons in the mesencephalon also revealed their multifaceted role (Matsumoto and Hikosaka, 2009). The classic hypothesis was that these neurons are activated by stimuli predicting reward and inhibited by aversive events (Schultz, 2007). If the properties of a more widespread population of these neurons are investigated in a Pavlovian paradigm with reward and punishment (liquid rewards and airpuffs directed at the face, respectively), two subpopulation of cells can be distinguished: some dopamine neurons are excited by reward-predicting stimuli and inhibited by punishment-predicting stimuli, whereas another groups of cells are excited by both of these stimuli. Neurons excited by the punishment-predicting stimuli were located dorsolaterally in the substantia nigra pars compacta, whereas those inhibited by the stimuli were located ventromedially, extending to the ventral tegmental area (Matsumoto and Hikosaka, 2009).

Our results raise the possibility that dopamine agonists used in the clinical practice may clearly affect only one aspect of these basic neuronal coding mechanisms in patients with PD: enhancing reward signals and diminishing punishment signals in the clinically used dose ranges for a longer period of time. The most likely explanation is that these drugs predominantly bind to D2/D3 receptors densely expressed in neurons coding reward signals (Lee et al., 2007). However, in this respect presynaptic and postsynaptic effects are hard to differentiate, and dose and treatment duration are essential. For example, a single low dose of a D2/D3 agonist pramipexole activates autoreceptors, reduces phasic dopamine release and impairs reward learning in humans (Santesso et al., 2009). These participants show pramipexole-induced feedback-related negativity to rewards and decreased activation in dorsal anterior cingulate cortex; disrupted reward learning is associated with reduced presynaptic dopaminergic signaling in response to reward (Santesso et al., 2009).

5.2.2. The possible clinical relevance of reward-learning and personality changes associated with dopamine agonists in PD

Although anecdotal reports suggest personality changes, i.e. decreased novelty seeking, rigidity, and neuroticism, well before the onset of PD motor symptoms (Menza, 2000), the data are not consistent and there are methodological uncertainties in these reports. Arabia et al. (2010) found that introversion and decreased novelty seeking do not predict PD in a community sample, whereas anxious temperament may represent a minor risk (Bower et al., 2010). However, the nature of anxious temperament is too general to be related to specific diseases and may be related to general health issues. Gatto et al. (2011) argued against the existence of a specific "Parkinsonian" personality pattern.

In a positron emission tomography study, Kaasinen et al. (2001) found that novelty seeking was not associated with (18)F-dopa uptake in any of the brain regions studied in patients with PD. Harm avoidance, which is closely related to anxious and depressive traits, was increased in PD patients and exhibited a positive correlation with the (18)F-dopa uptake in the right caudate nucleus.

Tomer and Aharon-Peretz (2004) suggested an interesting lateralization theory of personality changes in PD: patients with greater dopamine loss in the left hemisphere showed reduced novelty seeking, whereas patients with reduced dopamine in the right hemisphere reported higher harm avoidance. Kaasinen et al. (2004) found that decreased novelty seeking in PD patients may be related to altered dopaminergic transmission in the insula.

Our results from never-medicated, young, non-depressed patients showed that decreased novelty seeking and reward processing deficits are early signs of PD, although we can not claim that these changes appeared before the evolution of motor symptoms. Our sample was not large enough to test differences between patients with right- and left-sided motor symptoms, but many of our patients displayed right-sided symptoms (left-hemisphere dopamine deficiency), which is consistent with the results of Tomer and Aharon-Peretz (2004). Furthermore, dopaminergic replacement increased novelty seeking, which is similar to that found after deep-brain stimulation in PD (Fassino et al., 2010). Deep-brain stimulation of the subthalamic nucleus is also associated with increased reward-sensitivity and enhanced reinforcement learning (Frank et al., 2007).

In the current literature there is enormously increased attention to dopamine dysregulation syndrome (DDS) in PD, which is interpreted as a consequence of dysfunctional reward system due to dopamine replacement therapy. The symptoms can be varied from craving for dopaminergic medication to impulse control disorders (gambling, punding, hypersexuality, compulsive shopping, eating disorders, compulsive internet use), hypomania, and even psychosis (Evans and Lees, 2004; Merims and Giladi, 2008). Although neuropsychiatric complications associated with dopamine replacement were reported at the same time when L-dopa entered into clinical practice (Yahr et al., 1969), some authors believe that the increasing prevalence of DDS is due to the application of dopamine agonists (Perez-Lloret and Rascol, 2010). According to Bostwick et al. (2009), 18% of PD patients receiving dopamine agonists develop impulse control disorders, whereas in the case of L-dopa such problems are much more rare (<5%).

In the so far largest case-control study, Voon et al. (2011a) showed that impulse control disorder in PD is associated with general functional impairment, more severe anxiety and depression, obsessive-compulsive symptoms, dyskinesias, higher novelty seeking, impulsivity, and reward preference. These clinical observations are highly consistent with our results, also indicating increased novelty seeking and reward preference after the initiation of dopamine agonist medications. However, it is important to emphasize that none of the patients in our study showed DDS, which may indicate that biases in novelty seeking and reward sensitivity appear without the development of clinical symptoms. These changes in tests and TCI scores may reflect an endophenotype for DDS and in the future they may serve as vulnerability markers.

In addition to specific dysfunctions in reward processing and novelty seeking, DDS is associated with general neuropsychological deficits. Vitale et al. (2011) showed that PD patients with impulse control disorders scored lover on tasks for spatial planning and attentional set-shifting. Patients with hypersexuality, compulsive eating, and multiple impulsive symptoms performed worse on verbal learning and memory tests than did patients with pathological gambling. Punding may be a different form of DDS associated with the severity of dyskinesia, younger age at disease onset, longer disease duration, and male gender (Spencer et al., 2011).

Beyond reward, novelty seeking, and general neuropsychological functions what are the mechanisms of DDS? Using the Balloon Analogue Risk Task, Claassen et al. (2011) assessed PD patients with impulse control disorders when they received and when they ceased dopamine agonists. Dopamine agonists boosted risk taking only in patients with impulse control disorders, especially when doses were higher. However, both patients groups similarly reduced risk-taking choices in high risk conditions and after negative consequences.

To elucidate the neuronal mechanism of DDS in PD, Voon et al. (2011b) used a pharmacological functional neuroimaging method during a gambling task. As expected, patients with impulse control disorders executed more risky decision especially when there was likelihood to gain points (reward), which was associated with decreased orbitofrontal cortex and anterior cingulate activity. Healthy controls and PD patients without DDS showed the opposite pattern. After the administration of dopamine agonists, risky gain choices were increased in DDS patients, together with a decreased activity in the ventral striatum. Again, it was exactly the opposite in PD patients without DDS and healthy controls. These results highlight the importance of non-striatal regions in risk evaluation in DDS, and the fact that the ventral striatum exhibits a paradoxically decreased responsiveness after dopamine agonist challenge in DDS but not in PD without such neuropsychiatric complications.

5.3. Transfer and flexibility of stimulus-response associations in AD

5.3.1. Habit learning in AD, striatal automaticity, and hippocampal pattern completion

As expected on the basis of results from elderly persons with atrophy of the hippocampal region (Myers et al., 2002, 2003), patients with mild AD showed a robust impairment on the acquired equivalence test: in the transfer phase, they performed at the chance level in the case of new associations formed according to acquired equivalence but not prior learning, whereas they were able to learn and remember old associations similarly to controls. However, the representation of these well-trained associations was rigid, which were correctly retrieved in the computer-assisted forced-choice test. When associations were requested to be recalled using cards (fish-face pairs), patients with

AD showed deficient performances. This is especially striking because, after the card pairing test, patients again performed the computer test for associations as efficiently as did controls. This suggests that the representation of old associations is less flexible in AD patients and cannot be transferred to new retrieval conditions.

This feature of old associations is characteristic for habit learning. As proposed by Dickinson (1985), overtraining results in the development of behavior autonomy and to the formation of habits. Converging evidence from animal studies, human neuropsychology, and functional neuroimaging indicates that the basal ganglia play a crucial role in habit formation (Yin and Knowlton, 2006). Myers et al. (2003) found that patients with PD tested on their normal dopaminergic medication failed to learn associations during the training phase and committed a large number of errors on stimulus-response associations. PD patients who were able to learn the associations showed normal acquired equivalence, that is, their performance was spared in the case of new associations previously not learned during the feedback-guided training session (Myers et al., 2003). This suggests dissociation between striatal and medial temporal lobe memory systems.

However, not all results support this strict distinction, and it is likely that habit-like behavior is a not a unitary construct at the behavioral and neuronal level. As pointed out by Ashby et al. (2010) the classic view is that novel behavior is mediated by the cortex and rapidly encoded into declarative memory traces via cortico-hippocampal interaction; slow behavioral automaticity requires the transfer of processing to subcortical structures, with a special reference to the striatum. Now we know that neurons in the associative striatum are activated during early learning, which is similar to medial temporal lobe circuits, whereas those in the sensorimotor striatum are active after a longer training when automaticity has developed. In other cases, automatic and habit-like behaviors are striatum- and dopamine-independent (Ashby et al., 2010).

What is the contribution of the hippocampal region to acquired equivalence? One of the simplest explanations is Marr's pattern completion hypothesis (1971). According to this hypothesis, the hippocampus contains an autoassociative network, which consists of interconnected neurons that is able to quickly map a stimulus input (Kesner and Rolls, 2001). The simplest example of pattern completion is the property of CA3 hippocampal cells responding to a stimulus when a part of it is missing (e.g. a part

of space is hidden by darkness). In other words, the firing pattern of neuronal populations reflects a completion of the stimulus in the absence of the whole visual input. Rats with lesions to the CA3 and dentate gyrus, but not CA1, were impaired only when a subset of visual stimuli were present during the test phase of a spatial pattern completion task (Kirwan et al., 2005).

Acquired equivalence can be interpreted as a form of pattern completion in an autoassociative network. If neuronal populations code A – X, B – Y, and B – X associations, a simple completion mechanism can produce the A – Y association even if the organism was not exposed to this association before. This autoassociative pattern completion can be performed by the entorhinal cortex, dentate gyrus or the CA3 region. Information from the existing associations may be feedforwarded to the medial temporal lobe from the cortico-striatal system.

5.3.2. Is feedback-guided stimulus-response learning an implicit memory process?

Two previous studies also found spared feedback-guided stimulus-response learning in AD (Eldridge et al., 2002; Klimkowicz-Mrowiec et al., 2008). Klimkowicz-Mrowiec et al. (2008) used a classic probabilistic classification learning task in which associations between cards and weather outcome (rainy or sunny) must be learned based on feedback. Surprisingly, these authors found that AD patients with moderate explicit memory impairment performed the task significantly better than those with mild AD and controls. The authors interpreted their results as evidence for the competition between declarative (explicit) and procedural (implicit) memory systems in humans. If we assume that over-trained stimulus-response associations tap on the implicit memory system, then these results are in accordance with several other studies that found relatively preserved procedural memory in AD (Bondi and Kaszniak, 2001; Golby et al., 2005; Lustig and Buckner, 2004; van Halteren-van Tilborg et al., 2007).

The first compelling demonstration for intact implicit memory systems in elderly people and in dementia comes from Lustig and Buckner (2004) who used a repetition priming paradigm. The authors recruited 34 young adults, 33 older adults without dementia, and 24 older adults in the early stages of AD. Functional neuroimaging data revealed that both older adult groups showed response time reduction along repetition

(priming) and changes in activation in the inferior frontal gyrus, which was very similar to that seen in young adults.

Golby et al. (2005) investigated explicit encoding and retrieval of scenes, as well as priming for the same stimuli in early AD. At the behavioral level, AD patients showed deficits on recognition, whereas priming was spared. In the explicit condition, AD patients showed dysfunctional brain activation in the ventral visual stream participating in object and scene perception; the most impaired activation was seen in the medial temporal lobe and fusiform gyrus, whereas most preserved activations were measured in primary visual cortex. Behavioral performance in the explicit condition was predicted by activation of the medial temporal lobe and lingual/fusiform gyrus, whereas lateral occipital and parietal cortices accounted for priming performance.

Feedback-guided associative learning can not be considered as a full implicit task, because, especially at the beginning of the training session, participants make conscious effort to memorize associations. Indeed, in the initial stage of the training, there is hippocampal activation which is gradually replaced by increasing striatal activity (Poldrack et al., 2001). Bozoki et al. (2006) pointed the possibility that during category association tasks the comparison of patient and control groups is confounded by the contribution of more than one memory systems. Using functional magnetic resonance imaging, Johnson et al. (2008) examined dynamic neural responses during associative learning over trials. Results revealed hippocampal signal attenuation in parallel with effective learning in healthy participants, which may indicate that the role of the hippocampal memory system became less evident over trials. Intriguingly, patients with amnestic mild cognitive impairment, a clinical risk condition for AD, did not show such attenuation, which may be a compensatory phenomenon of inefficiently functioning in the hippocampal formation (Johnson et al., 2008). deRover et al. (2011) found a similar hyperactivity in atrophized medial temporal regions of patients with mild cognitive impairment using a paired associates learning task.

One of the most widespread implicit stimulus-response learning procedures in the motor domain is the serial reaction time task. During this task, participants are requested to learn a series of associations between a fixed order of visual stimuli (e.g., location of flashing squares on the screen) and a particular motor response (e.g., pressing buttons). The order of visual stimuli is unknown for the participants and

remains outside the field of consciousness, but despite this implicit nature of the task, reaction time will be speeded along with training sessions. Based on the studies discussed above, we may expect preserved serial reaction time learning in AD and impaired learning in PD. Early studies showed that this is the case (e.g., Ferraro et al., 1993), which was confirmed by a meta-analysis (Siegert et al., 2006) and direct comparison of AD and PD patients on different version of the task (van Tilborg AND Hulstijn, 2010) However, implicit learning capacity strongly depends on the severity of AD symptoms and on the possible executive component of the tasks (Logie et al., 2004), which can be a disturbing and irrelevant variable in this context.

An important confounding factor is that the same stimulus-response categorization task can be acquired in different ways depending, for example, on the task instructions and the encoding strategy used by the participant. This hypothesis was directly investigated (Gureckis et al., 2011). Following incidental learning of category members, a deactivation in the visual cortex can be detected in response to novel exemplars of a learned category. The activity is influenced by stimulus-encoding strategies, which can be modulated simply by task instructions. When participants are asked to listen to the shape and size of stimuli during learning, sensory cortical deactivation, a signature of implicit learning, is absent. Therefore, the same learning procedure can be executed in different ways depending on the strategy used by the participant (Gureckis et al., 2011).

Another problem is that, as mentioned in the introduction, neurodegenerative processes often cross the boundary of classic diagnostic categories (Armstrong, 2005). This is true for the localization of lesion. For instance, Kalaitzakis et al. (2008) detected striatal beta-amyloid deposition in PD with dementia. Colla et al. (2003) identified a subgroup of AD patients with altered metabolism in the basal ganglia who showed deficits on the learning of probabilistic associations. Similarly, Ferraro et al. (1993) demonstrated impaired implicit learning of associations during a serial reaction time task in both AD and PD patients. In our study, only three AD patients were not able to complete the feedback-guided training phase and although the completer patients who passed the training phase still committed more training errors than controls, their performance was much better that that of patients with PD reported in the literature (Myers et al., 2003).

It is also important that the accumulation of abnormal proteins and brain volume loss are not the same (Tosun et al., 2011). Amyloid-β accumulation may be the earliest events in AD, possibly leading to direct synaptic dysfunction and later neurodegeneration. Amyloid-β accumulation can be visualized by (11)C-labeled Pittsburgh compound positron emission tomography (PET). The relationship between protein deposition and atrophy is not linear: increased amyloid-β burden in the left precuneus/cuneus and medial-temporal regions is associated with accelerated atrophy in the left medial-temporal and parietal regions, whereas increased amyloid-β burden in bilateral precuneus/cuneus and parietal regions is associated with atrophy in the right medial temporal regions. Therefore, protein accumulation, possibly having a direct negative effect of synaptic transmission, and brain atrophy affect different brain regions and hence may have a negative impact on different memory systems (Tosun et al., 2011).

The overlap between neurodegenerative diseases and the heterogeneity of cases may lead to contradictory results. For example, the simple distinction that explicit memorization of stimulus-response associations is disrupted in AD but spared in PD, whereas the feedback-guided gradual acquisitions of these associations is relatively spared in AD but disrupted in PD has not been replicated in each study, and it seems that the phenomenon is definitely task-dependent (e.g., the response requirements of the task). For example, if we modify the feedback after responding by removing time limits on responding and hence delaying the effect of feedback, PD patients will be non-impaired (Wilkinson et al., 2008), whereas AD patients will be impaired. Basically, it is not surprising because delayed feedback is similar to trace conditioning requiring the intact functioning of the hippocampal formation (McEchron and Disterhoft, 1999).

In conclusion, our results suggest that the impairment of acquired equivalence associative learning is an extremely sensitive marker of cognitive decline even in mild AD: whereas feedback-guided associative learning was only mildly affected, AD patients performed at the chance level in the acquired equivalence condition. These data allow new insight into the functioning of the hippocampal complex and may provide a new tool for the refinement of the clinical diagnosis of AD.

5.4. Visuospatial functions discriminate between AD and FTD

We found that both global scores and specific errors on the CDT discriminated AD patients from FTD patients. As expected, AD patients showed poorer performances as compared to FTD patients. Therefore, it is likely that neocortical degeneration affecting the posterior association cortex in AD is a more prominent contributor to CDT deficit than the executive deficit associated with FTD. However, there was a considerable overlap between the two groups at the level of individual patients, and therefore in the clinical practice we can meet with FTD patients with AD-type CDT performance and AD patients with FTD-type CDT performance.

However, the qualitative error analysis specifically demonstrated that the FTD group had fewer visuospatial deficits than the AD group, which was especially prominent in the case of the spatial layout of numbers. This is consistent with the above-described conclusion that AD patients show more severe visuospatial deficits, which is the consequence of posterior neocortical degeneration. However, structural neuroimaging procedures were not used in our study, therefore this inference remains indirect. Elfgren et al. (1994) also found that AD patients show more severe visuospatial deficits than FTD patients by using other neuropsychological tests. Tranel et al. (2008) found correlation between posterior parietal volume and CDT performance in patients with widespread brain lesions.

Another major discriminating error type was conceptual errors, which was also more pronounced in AD compared to FTD. According to Rouleau et al. (1992) this type of error is due to the loss of semantic knowledge related to the concept of "clock" in AD, which is another consequence of neocortical damage, but in this case affecting the left hemisphere. Using positron emission tomography, Vandenberghe et al. (1996) delineated how conceptual knowledge is related to visuospatial information in the brain. The authors contrasted regional cerebral blood flow during two semantic tasks (probing knowledge of associations between concepts, and knowledge of the visual attributes of these concepts). There were modality specific activation foci; for words the left inferior parietal lobule and for pictures the right middle occipital gyrus. A modality-independent semantic network activated by both words and visual features was found from the left superior occipital gyrus through the middle and inferior temporal cortex to the inferior

frontal gyrus. When visual information must be used in a conceptual task, similarly to the CDT, the left posterior inferior temporal cortex was activated.

How do AD-related early changes affect the neuronal correlates of conceptual knowledge? Nelissen et al. (2007) used a combined functional magnetic resonance imaging and positron emission tomography approach to elucidate this issue. In the functional imaging part, two functions were compared: associative-semantic versus visuoperceptual decisions for words versus pictures. Beta-amyloid load was measured with the Pittsburgh Compound B (11C-PIB). AD patients exhibited an activation deficit in the posterior left superior temporal sulcus during the associative-semantic vs. visuoperceptual task, which was more pronounced for words than for pictures. This dysfunction was not independent of amyloid load: smaller responses were associated with higher amyloid load. Paradoxically, in the right posterior superior temporal cortex AD patients showed hyperactivation during the associative-semantic versus the visuoperceptual task. Critically, object naming performance in AD was predicted by the activation of the right posterior cortex, which indicates that visuospatial alterations are indeed related to semantic disturbances (Nelissen et al., 2007).

In the seminal study of Rouleau et al. (1992), AD patients showed a reliable improvement on CDT in the copy condition, which is based on simple perceptual but not conceptual or memory abilities of visuospatial recall. The command condition used during our assessment requires language for understanding, memory and conceptualization for the visual layout of a clock and the various time settings, and therefore this task is more difficult than the copy version (Freedman et al., 1994). The command condition moves beyond the functional testing of the posterior parietal lobe damage (visuospatial deficits), and may activate the more widespread semantic network described by Vandenberghe et al. (1996).

Contrary to our expectations and hypotheses, AD patients showed more executive-type errors on the CDT compared to FTD patients despite the fact that FTD patients are believed to exhibit a more severe executive deficit because of the frontal lobe damage (Pachana et al., 2006). Royall et al. (1998) conceptualized the “CLOX” format in order to specifically investigate executive deficits on CDT errors. One of the most frequently considered error type in this respect is the “frontal pull” response. However, “frontal pull” can be a consequence of comprehension problem and

grammatical failure to understand item relations (e.g., “10 *after* 11” for “10 *to* 11”). However, Cosentino et al. (2004) pointed to the fact that it is extremely difficult to related CDT measures to common tests of executive functions and semantic memory, probably because of the complex nature of the CDT requiring the interaction of overlapping cognitive functions.

Recently, Woodward et al. (2010) delineated a frontal variant of AD showing similar symptoms and neuropsychological profile to FTD patients. The frontal AD patients are more severely impaired than the non-frontal AD patients on most of the clinical measures, but behavioral signs, as measured with the Neuropsychiatric Inventory, are still less prominent than that observed in FTD patients. The frontal AD patients and FTD patients show very similar CDT performances, whereas non-frontal AD patients are less impaired on this test. This suggests that in the case of prominent frontal impairment, the difference between AD and FTD patients regarding CDT can be minimal (Woodward et al., 2010).

It is possible that modified versions of the CDT would be better to discriminate different types of dementias. One possible tool is the Clock Reading Test, which basically relies on visuospatial functions and eliminates the executive load of the CDT. To date the largest study compared 200 patients with dementias, 105 subjects with mild cognitive impairment, and 20 subjects with focal parietal lesions (Schmidtke and Olbrich, 2007). Whereas CDT was not appropriate to delineate the research groups, clock reading was impaired only in AD, parietal lesions, and Lewy Body Dementia, which is characterized by a severe visuospatial deficit. Healthy participants and FTD patients performed normally (Schmidtke and Olbrich, 2007).

Tuokko et al. (1992) suggested a combined Clock Test that has been further developed and validated. It assesses visuospatial abilities and abstract conceptualization and comprehension with three subtests: Clock Drawing, Clock Setting and Clock Reading. It is more sensitive than CDT alone and suitable for scoring several types of errors: omissions, misplacements, substitutions, rotations, distortions, perseveration, and additions. The test is validated in more than one thousand elderly individuals and exhibits a high level of inter-rater and test-retest reliability. Therefore, for future clinical applications this integrated approach could be very useful.

6. CONCLUSIONS

One of the most important questions in clinical neuroscience and neuropsychology is whether it is possible to selectively assess certain cognitive function and whether these functions can be disrupted in a circumscribed manner in neuropsychiatric diseases. This is the issue of domain specificity vs. non-specificity (Fodor, 1981) and selective vs. generalized cognitive deficits (Caramazza, 1992; Kosslyn and Intriligator, 1992).

In the first part of our experiments, we investigated feedback-guided learning of stimulus-response associations in PD and AD emphasizing three putatively specific functions: (i) effect of positive vs. negative feedback, (ii) generalization of associations (acquired equivalence), and (iii) flexibility of stimulus-response association. In the second part of the experiments, we investigated how CDT, a widely used classic neuropsychological test, is able to separate different cognitive domains (visuospatial functions, verbal comprehension, and executive functions) and how it can be used for the differentiation of AD and FTD.

Regarding positive vs. negative feedback (reward vs. punishment) we found a convincing dissociation: PD patients showed reward learning deficit and intact punishment learning, which was reversed by pharmacological manipulation. Stimulus-response learning and generalization were also dissociated; moreover, in patients with AD the retrieval of successfully learned stimulus-response associations was impaired in a context requiring cognitive flexibility. However, in the case of CDT domain specificity was not clear: this test includes many overlapping cognitive functions that can be separated only partly by scoring different types of errors.

The main conclusion is that novel neuropsychological tools must be more carefully designed, taking into consideration recent advances in cognitive neuroscience. The stimulus-response learning paradigms introduced in this thesis might represent good examples for such developments. We propose that by the application of these novel methods in clinical practice, domain-specific alterations can be detected in early phases of neuropsychiatric disorders, which may facilitate timely and objective diagnosis and help avoid delays in treatment administration.

7. SUMMARY

Neurodegenerative diseases comprise one of the major public health concerns in our aging population. Parkinson's disease (PD), Alzheimer's disease (AD) and frontotemporal dementia (FTD) are characterized by marked cognitive dysfunctions. The aim of our study was to find neuropsychological assessements which could be the early indicators of selective deficits of these dementias and the connected brain structures.

PD is characterized by the degeneration of dopaminergic pathways projecting to the striatum. These pathways are implicated in reward prediction. In this study, we investigated reward and punishment processing in young, never-medicated (nmed) PD patients, recently-medicated (med PD) patients receiving the dopamine receptor agonists pramipexole and ropinirole, and healthy controls. The nmed PD patients were also re-evaluated after 12 weeks of treatment with dopamine agonists. Reward and punishment processing was assessed by a feedback-based probabilistic classification task that enabled us to investigate stimulus-response learning guided by positive and negative feedback. Personality characteristics were measured by the Temperament and Character Inventory (TCI).

Acquired equivalence is a phenomenon in which prior training to treat two stimuli as equivalent increases generalization between them. Previous studies demonstrated that the hippocampal complex may play an important role in acquired equivalence associative learning. We investigated feedback-guided stimulus-response learning in early AD and tested the generalization and flexibility of these associations. The data analysis was focused on acquired equivalence and on the retrieval of associations in a free task context (non-directed card pairing) instead of instrumental responding.

The clock drawing test (CDT) is a widely used cognitive screening test. We investigated that the command condition of the CDT was able to discriminate between AD, FTD and controls. We examined quantitative (global) and qualitative (specific error type) differences. The data analysis was focused on errors related to visuospatial difficulties and conceptual problems, as visuospatial skill can be relatively preserved in FTD patients, and AD patients are expected to display more conceptual errors.

Results revealed that nmed PD patients showed selective deficits on reward processing and novelty seeking, which were remediated by dopamine agonists. These medications disrupted punishment processing. In addition, dopamine agonists increased the correlation between reward processing and novelty seeking, whereas these drugs decreased the correlation between punishment processing and harm avoidance. Our finding that dopamine agonist administration in young patients with PD resulted in increased novelty seeking, enhanced reward processing, and decreased punishment processing may shed light on the cognitive and personality bases of the impulse control disorders, which arise as side effects of dopamine agonist therapy in some PD patients.

Patients with early AD exhibited mild impairments in the training phase , they were able to learn stimulus-response associations using trial-by-trial feedback following decisions. Generalization of these associations, as measured by acquired equivalence, was impaired. Associative knowledge could not be transferred to a more flexible retrieval condition requiring flexible declarative knowledge. These results suggest that acquired equivalence learning is a markedly sensitive marker of early AD which may indicate the pathology of the hippocampal complex.

In the CDT investigations both global and error analysis helped discriminate the FTD group from controls and AD patients. Results showed significantly lower overall scores in the dementia groups compared to the control group, whereas FTD patients scored significantly higher than the AD group. On qualitative analysis, the FTD group had fewer stimulus bound responses, conceptual deficits, and spatial or planning errors compared to the AD group.

7. ÖSSZEFOGLALÁS

A Parkinson-kór (PD), az Alzheimer-kór (AD) és a frontotemporális-demencia (FTD) jelentős kognitív hanyatlást mutató kórképek. Vizsgálataink során olyan neuropszichológiai teszteket alkalmaztunk, amelyek érzékenyen jelzik ezen demenciák szelektív deficitjeit és a hozzájuk kapcsolódó agyi lokalizációk funkcióját.

A PD a striatális dopaminerg pályák degenerációját mutatja. Ezek a pályák vesznek részt a jutalomfüggő válasz kialakításában. Jelen kutatásunkban a jutalom- és a büntetés-érzékenységet kutattuk fiatal, soha nem kezelt PD, dopamin receptor agonista (DA) pramipexol és ropinirol gyógyszert szedő PD és egészséges kontroll személyeken. A nem kezelt betegeken a teszt illesztett változatait 12 héttel a DA gyógyszer beállítást követően ismételten felvettük. A jutalom- és büntetésérzékenység felmérését a stimulus-válasz tanulás vizsgálatát lehetővé tevő pozitív- negatív feedback alapú QUARTERS-teszt segítségével végeztük. A személyiség-karakter vizsgálatára a Cloninger-féle Temperamentum és Karakter Kérdőívet (TCI) is felvettük.

A tanult ekvivalencia jelenségének lényege, hogy ha két inger egymással ekvivalens, azaz ugyanazzal a válasszal kapcsolódik, akkor növekszik a velük kapcsolatos generalizációs képesség. Korábbi tanulmányok a hippocampus szerepét írták le a tanult ekvivalencia - asszociatív tanulási folyamatokban. Megvizsgáltuk a feedback-vezérelt stimulus-válasz tanulási folyamatokat korai AD-ban és az elsajátított asszociációk generalizációs és flexibilitási jellemzőit. Adataink feldolgozása során a tanult ekvivalenciára és a kontextus - reprezentációra (kártyaválogatás) összpontosítottunk.

Az óra rajzolási teszt (CDT) egy széles körben alkalmazott kognitív vizsgáló eljárás. Tanulmányoztuk, hogy az irányított CDT képes-e az AD, FTD és a kontroll csoportok között különbséget tenni. Mennyiségi (globális) és minőségi (specifikus) különbségeket kerestünk. Elsősorban a vizuális-téri- és a fogalmi nehézségekből adódó hibákat kutattuk, mivel FTD betegeknél a vizuális-téri képességek viszonylag megtartottak, míg az AD betegek számos konceptuális hibát ejtenek.

Eredményeink szerint a nem kezelt PD betegek a jutalomérzékenység és az újdonságkeresés szelektív deficitjét mutatták, mely a DA kezelés hatására változott. Ezek a gyógyszerek a büntetés-érzékenységet negatív irányba módosították. Továbbá a

DA kezelés emelte a jutalomfüggő válasz és az újdonságkeresés közti összefüggést, ellenben a büntetésfüggő válasz és az ártalom-kerülés közti korrelációt rontották. A DA szerek a fiatal PD betegekben az újdonságkereső magatartást fokozták, javították a jutalomérzékenységet, ellenben a büntetés-érzékenységük romlott. Eredményeink alapján felmerül, hogy a PD betegeknél esetenként jelentkező impulzus kontroll zavar alapja a DA terápia mellékhatásaként jelentkező kognitív- és személyiség-változás lehet.

Korai AD betegek vizsgálatai során a tanulási fázisban enyhe deficitet találtunk, a stimulus-válasz asszociációkat el tudták sajátítani a visszajelzések alapján, azonban a megtanult asszociációkat nem tudták generalizálni (tanult ekvivalencia). Az információ deklaratív tudást igénylő, új és flexibilisebb formában történő előhívása, alkalmazása károsodott. Eredményeink alapján a tanult ekvivalencia zavara szenzitív markere lehet a korai hippocampus károsodásnak korai AD-ban.

A CDT-vel folytatott vizsgálataink során a FTD jól elkülöníthetőnek bizonyult mind a globális, mind a specifikus hiba - analízisek alapján a kontroll és az AD személyektől is. Eredményeink alapján a demencia csoportok szignifikánsan rosszabbul teljesítettek a kontrollokhoz képest, bár a FTD betegek magasabb pontokat értek el, mint az AD személyek. A minőségi elemzés során azt találtuk, hogy a FTD csoport kevesebbet hibázott a stimulus-kötött, a fogalmi- és a téri vagy a tervezési elemzés során összehasonlítva az AD csoporttal.

8. REFERENCES

Arabia G, Grossardt BR, Colligan RC, Bower JH, Maraganore DM, Ahlskog JE, Geda YE, Rocca WA. Novelty seeking and introversion do not predict the long-term risk of Parkinson disease. Neurology 2010;75:349-357.

Armstrong RA, Lantos PL, Cairns NJ. Overlap between neurodegenerative disorders. Neuropathology 2005;25:111-124.

Ashby FG, Turner BO, Horvitz JC. Cortical and basal ganglia contributions to habit learning and automaticity. Trends Cogn Sci 2010;14:208-215.

Au WL, Zhou J, Palmes P, Sitoh YY, Tan LC, Rajapakse JC. Levodopa and the feedback process on set-shifting in parkinson's disease. Hum Brain Mapp 2011, doi: 10.1002/hbm.21187. [Epub ahead of print]

Bassetti CL. Nonmotor disturbances in Parkinson's disease. Neurodegener Dis 2011;8:95-108.

Bereczki D. The description of all four cardinal signs of Parkinson's disease in a Hungarian medical text published in 1690. Parkinsonism Relat Disord 2010;16:290-293.

Berridge KC. The debate over dopamine's role in reward: the case for incentive salience. Psychopharmacology (Berl) 2007;191:391-431.

Bolikal P, Myers CE, Patel R, Ropp L, Daw N, Gluck MA. Punishment-based learning correlates with a putative index of serotonin in healthy young adults. Cognitive Neuroscience Society Annual Meeting Program, 2007, F148. [abstract]

Bondi MW, Kaszniak AW. Implicit and explicit memory in Alzheimer's disease and Parkinson's disease. J Clin Exp Neuropsychol 1991;13:339-358.

Bonelli RM, Cummings JL. Frontal-subcortical dementias. Neurologist 2008;14:100-107.

Bostwick JM, Hecksel KA, Stevens SR, Bower JH, Ahlskog JE. Frequency of new-onset pathologic compulsive gambling or hypersexuality after drug treatment of idiopathic Parkinson disease. Mayo Clin Proc 2009;84:310-316.

Bowler JV, Wade JP, Jones BE, Nijran KS, Steiner TJ. Natural history of the spontaneous reperfusion of human cerebral infarcts as assessed by 99mTc HMPAO SPECT. J Neurol Neurosurg Psychiatry. 1998 Jan;64(1):90-7.

Bozoki A, Grossman M, Smith EE. Can patients with Alzheimer's disease learn a category implicitly? Neuropsychologia 2006;44:816-827.

Bozoki AC, Farooq MU. Frontotemporal lobar degeneration insights from neuropsychology and neuroimaging. Int Rev Neurobiol 2009;84:185-213.

Brickman AM, Stern Y, Small SA. Hippocampal subregions differentially associate with standardized memory tests. Hippocampus 2010 Sep 7. [Epub ahead of print]

Bromberg-Martin ES, Matsumoto M, Hikosaka O. Dopamine in motivational control: rewarding, aversive, and alerting. Neuron 2010;68:815-834.

Brun A. Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. Arch Gerontol Geriat 1987;6:193–208.

Bradshaw JL, Sheppard DM. The neurodevelopmental frontostriatal disorders: evolutionary adaptiveness and anomalous lateralization. Brain Lang 2000;73:297-320.

Cahn-Weiner DA, Williams K, Grace J, Tremont G, Westervelt H, Stern RA. Discrimination of dementia with lewy bodies from Alzheimer disease and Parkinson disease using the clock drawing test. Cogn Behav Neurol 2003;16:85–92.

Caramazza A. Is cognitive neuropsychology possible? J Cogn Neurosci 2003;4:80-95.

Cirino PT, Chin CE, Sevcik RA, Wolf M, Lovett M, Morris RD. Measuring socioeconomic status: reliability and preliminary validity for different approaches. Assessment 2002; 9: 145-155.

Claassen DO, van den Wildenberg WP, Ridderinkhof KR, Jessup CK, Harrison MB, Wooten GF, Wylie SA. The risky business of dopamine agonists in Parkinson disease and impulse control disorders. Behav Neurosci 2011;125:492-500.

Cloninger RC. The temperament and character inventory (TCI): A guide to its development and use. St. Louis, MO: Center for Psychobiology of Personality, Washington University, 1994.

Colla M, Ende G, Bohrer M, Deuschle M, Kronenberg G, Henn F, Heuser I. MR spectroscopy in Alzheimer's disease: gender differences in probabilistic learning capacity. Neurobiol Aging 2003;24:545-552.

Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex 2001;11:1136–1143.

Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia 2003;41:1431–1441.

Cools R, Altamirano L, D'Esposito M. Reversal learning in Parkinson's disease depends on medication status and outcome valence. Neuropsychologia 2006;44:1663-1673.

Cosentino S, Jefferson A, Chute DL, Kaplan E, Libon DJ. Clock drawing errors in dementia: neuropsychological and neuroanatomical considerations. Cogn Behav Neurol 2004;17:74-84.

Coutureau E, Killcross AS, Good M, Marshall VJ, Ward-Robinson J, Honey RC. Acquired equivalence and distinctiveness of cues: II. Neural manipulations and their implications. J Exp Psychol Anim Behav Proc 2002;28: 388-396.

Crum RM, Anthony JC, Bassett SS, Folstein MF. Population-based norms for the Mini-Mental State Examination by age and educational level. JAMA. 1993 May 12;269(18):2386-91.

de Rover M, Pironti VA, McCabe JA, Acosta-Cabronero J, Arana FS, Morein-Zamir S, Hodges JR, Robbins TW, Fletcher PC, Nestor PJ, Sahakian BJ. Hippocampal dysfunction in patients with mild cognitive impairment: A functional neuroimaging study of a visuospatial paired associates learning task. Neuropsychologia 2011;49:2060-2070.

deToledo-Morrell L, Stoub TR, Wang C. Hippocampal atrophy and disconnection in incipient and mild Alzheimer's disease. Prog Brain Res 2007;163:741-753.

Dickinson A. Actions and habits: the development of behavioural autonomy. Philos Trans R Soc Lond, Biol Sci 1985;308: 67–78.

Düzel E, Bunzeck N, Guitart-Masip M, Wittmann B, Schott BH, Tobler PN. Functional imaging of the human dopaminergic midbrain. Trends Neurosci 2009;32:321-328.

Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. Annu Rev Neurosci 2007;30:123-152.

Eldridge LL, Masterman D, Knowlton BJ. Intact implicit habit learning in Alzheimer’s disease. Behav Neurosci 2002;116:722–726.

Elfgren C, Brun A, Gustafson L, Johanson A, Minthon L, Passant U, Risberg J. Neuropsychological tests as discriminators between dementia of Alzheimer's type and Frontotemporal dementia. Int J Ger Psychiat 1994;9:635– 642.

Ellis HC, Feugre RL, Long KK, Pegram VG. Evidence for acquired equivalence of cues in perceptual tasks. Percept Mot Skills 1964;19:159-162.

Ena S, de Kerchove d'Exaerde A, Schiffmann SN. Unraveling the differential functions and regulation of striatal neuron sub-populations in motor control, reward, and motivational processes. Front Behav Neurosci 2011;5:47.

Evans AH, Lees AJ. Dopamine dysregulation syndrome in Parkinson's disease. Curr Op Neurol 2004;17:393–398.

Fassino S, Abbate Daga G, Gramaglia C, Pierò A, Zibetti M, Castelli L, Cinquepalmi A, La Notte M, Lopiano L. Novelty-seeking in Parkinson's disease after deep brain stimulation of the subthalamic nucleus: a case-control study. Psychosomatics 2010;51:62-67.

Ferraro FR, Balota DA, Connor LT. Implicit memory and the formation of new associations in nondemented Parkinson's disease individuals and individuals with senile dementia of the Alzheimer type: a serial reaction time (SRT) investigation. Brain Cogn 1993;21:163-180.

Finder VH. Alzheimer's disease: a general introduction and pathomechanism. J Alzheimers Dis 2010;22(Suppl 3):5-19.

Fodor JA. Representations: Philosophical Essays on the Foundations of Cognitive Science. Cambridge, MIT, 1981.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975 Nov;12(3):189-98.

Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 2004;306:1940-1943.

Frank MJ, O'Reilly RC. A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. Behav Neurosci 2006;120:497-517.

Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 2007;318:1309-1312.

Frank S, Clavaguera F, Tolnay M. Tauopathy models and human neuropathology: similarities and differences. Acta Neuropathol 2008;115:39-53.

Freedman M, Leach L, Kaplan E, Shulman KI, Delis DC. Clock drawing: A neuropsychological analysis. New York: Oxford University Press, 1994.

Fukui T, Lee E, Kitamura M, Hosoda H, Bokui C, Ikusu K, Okita K. Visuospatial dysfunction may be a key in the differentiation between Alzheimer's disease and subcortical cognitive impairment in moderate to severe stages. Dement Geriatr Cogn Disord 2009;28:288-294.

Galariotis V, Bódi N, Janka Z, Kálmán J. Frontotemporal dementia -Part II. Differential diagnosis, genetics, molecular pathomechanism and pathology. Ideggyogy Szle 2005;58:220-224.

Gatto NM, Bordelon Y, Gatz M, Ritz B. Personality characteristics and motor skills attributed to occupations in Parkinson disease. Cogn Behav Neurol 2011;24:18-25.

Gibb WR, Lees AJ. A comparison of clinical and pathological features of young- and old-onset Parkinson's disease. Neurology 1988;**38:**1402–1406.

Golby A, Silverberg G, Race E, Gabrieli S, O'Shea J, Knierim K, Stebbins G, Gabrieli J. Memory encoding in Alzheimer's disease: an fMRI study of explicit and implicit memory. Brain 2005;128:773-787.

Gotham AM, Brown RG, Marsden CD. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain 1988;111: 299-321.

Graef S, Biele G, Krugel LK, Marzinzik F, Wahl M, Wotka J. Differential influence of levodopa on reward-based learning in Parkinson's disease. Front Hum Neurosci 2010;4:169.

Hanseeuw B, Dricot L, Kavec M, Grandin C, Seron X, Ivanoiu A. Associative encoding deficits in amnestic mild cognitive impairment: a volumetric and functional MRI study. Neuroimage 2011;56:1743-1748.

Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967; 17: 427-442.

Honey RC, Hall G. Acquired equivalence and distinctiveness of cues. J Exp Psychol Anim Behav Process 1989;15:338-346.

Ino T, Asada T, Ito J, Kimura T, Fukuyama H. Parieto-frontal networks for clock drawing revealed with fMRI. Neurosci Res 2003;45:71-77.

Jacobs H, Heberlein I, Vieregge A, Vieregge P. Personality traits in young patients with Parkinson's disease. Acta Neurol Scand 2001;103:82-87.

Jahanshahi M, Wilkinson L, Gahir H, Dharminda A, Lagnado DA. Medication impairs probabilistic classification learning in Parkinson's disease. Neuropsychologia 2010;48:1096-1103.

Jellinger KA. Neuropathological aspects of Alzheimer disease, Parkinson disease and frontotemporal dementia. Neurodegener Dis 2008;5:118-121.

Jensen J, Smith AJ, Willeit M, Crawley AP, Mikulis DJ, Vitcu I, Kapur S. Separate brain regions code for salience vs. valence during reward prediction in humans. Hum Brain Mapp 2007;28:294-302.

Johnson SC, Schmitz TW, Asthana S, Gluck MA, Myers C. Associative learning over trials activates the hippocampus in healthy elderly but not mild cognitive impairment. Neuropsychol Develop Cogn B Aging Neuropsychol Cogn 2008;15:129-145.

Jubault T, Brambati SM, Degroot C, Kullmann B, Strafella AP, Lafontaine AL,Chouinard S, Monchi O. Regional brain stem atrophy in idiopathic Parkinson's disease detected by anatomical MRI. PLoS One 2009;4:e8247.

Juckel G, Schlagenhauf F, Koslowski M, Filonov D, Wüstenberg T, Villringer A, Knutson B, Kienast T, Gallinat J, Wrase J, Heinz A. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. Psychopharmacology (Berl) 2006;187:222-228.

Kaasinen V, Nurmi E, Bergman J, Eskola O, Solin O, Sonninen P, Rinne JO. Personality traits and brain dopaminergic function in Parkinson's disease. Proc Natl Acad Sci USA 2001;98:13272-13277.

Kaasinen V, Aalto S, Någren K, Rinne JO. Insular dopamine D2 receptors and novelty seeking personality in Parkinson's disease. Mov Disord 2004;19:1348-1351.

Kalaitzakis ME, Graeber MB, Gentleman SM, Pearce RK. Striatal beta-amyloid deposition in Parkinson disease with dementia. J Neuropathol Exp Neurol 2008;67:155-161.

Kesner RP, Rolls ET. Role of long-term synaptic modification in short-term memory. Hippocampus 2001;11:240–250.

Kéri S, Moustafa AA, Myers CE, Benedek G, Gluck MA. Alpha-synuclein gene duplication impairs reward learning. Proc Natl Acad Sci USA 2010;107:15992-15994.

Kertesz A, Munoz DG. Pick's disease and Pick complex. New York: Wiley-Liss, 1998.

Kertesz A, McMonagle P, Blair M, Davidson W, Munoz DG. The evolution and pathology of frontotemporal dementia. Brain 2005;128.1996–2005.

Kirwan CB, Gilbert PE, Kesner RP. The role of the hippocampus in the retrieval of a spatial location. Neurobiol Learn Mem 2005;83:65-71.

Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. N Engl J Med 1988;318:876–880.

Klimkowicz-Mrowiec A, Slowik A, Krzywoszanski L, Herzog-Krzywoszanska R, Szczudlik A. Severity of explicit memory impairment due to Alzheimer's disease improves effectiveness of implicit learning. J Neurol 2008;255:502-509.

Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. Science 1996;273:1399-1402.

Kobayakawa M, Tsuruya N, Kawamura M. Sensitivity to reward and punishment in Parkinson's disease: an analysis of behavioral patterns using a modified version of the Iowa gambling task. Parkinsonism Relat Disord 2010;16:453-457.

Korczyn AD, Reichmann H. Dementia with Lewy bodies. J Neurol Sci 2006;248:3-8.

Kosslyn SM, Intriligator JM. 1992. Is cognitive neuropsychology plausible? The perils of sitting on a one-legged stool. J Cogni Neurosci 1992;4:96-105.

Krebs RM, Schott BH, Düzel E. Personality traits are differentially associated with patterns of reward and novelty processing in the human substantia nigra/ventral tegmental area. Biol Psychiatry 2009;65:103-110.

Kvernmo T, Härtter S, Burger E. A review of the receptor-binding and harmacokinetic properties of dopamine agonists. Clin Ther 2006;28:1065-1078.

Launer LJ, Andersen K, Dewey ME, Letenneur L, Ott A, Amaducci LA, Brayne C, Copeland JR, Dartigues JF, Kragh-Sorensen P, Lobo A, Martinez-Lage JM, Stijnen T, Hofman A. Rates and risk factors for dementia and Alzheimer's disease: results from EURODEM pooled analyses. EURODEM Incidence Research Group and Work Groups. European Studies of Dementia. Neurology 1999;52:78-84.

Lang AE, Fahn S. Assessment of Parkinson's disease. In: Munsat TL, ed. Quantification of Neurologic Deficit. Boston, Mass: Butterworth-Heinemann, 1989, pp. 285-309.

Laurén J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature 2009;457:1128-1132.

Lee B, Groman S, London ED, Jentsch JD. Dopamine D2/D3 receptors play a specific role in the reversal of a learned visual discrimination in monkeys. Neuropsychopharmacology 2007;32:2125-2134.

Lees AJ, Hardy J, Revesz T. Parkinson's disease. Lancet 2009;373:2055-2066.

Levy-Gigi E, Kelemen O, Gluck MA, Kéri S. Impaired context reversal learning, but not cue reversal learning, in patients with amnestic mild cognitive impairment. Neuropsychologia 2011 Aug 11. [Epub ahead of print]

Logie RH, Cocchini G, Delia Sala S, Baddeley AD. Is there a specific executive capacity for dual task coordination? Evidence from Alzheimer's disease. Neuropsychology 2004;18:504-513.

Lustig C, Buckner RL. Preserved neural correlates of priming in old age and dementia. Neuron 2004;42:865-875.

MacDonald PA, Macdonald AA, Seergobin KN, Tamjeedi R, Ganjavi H, Provost JS. The effect of dopamine therapy on ventral and dorsal striatum-mediated cognition in Parkinson's disease: support from functional MRI. Brain 2011;134:1447-1463.

Maia TV, Frank MJ. From reinforcement learning models to psychiatric and neurological disorders. Nat Neurosci 2011;14:154-162.

Marr D. Simple memory: a theory for archicortex. Philos Trans Roy Soc Lond B, Biol Sci 1971;262:23–81.

Matsuoka T, Narumoto J, Shibata K, Okamura A, Nakamura K, Nakamae T, Yamada K, Nishimura T, Fukui K. Neural correlates of performance on the different scoring systems of the clock drawing test. Neurosci Lett 2011;487:421-425.

McEchron MD, Disterhoft JF. Hippocampal encoding of non-spatial trace conditioning. Hippocampus 1999;9:385-396.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984 Jul;34(7):939-44.

Mehler-Wex C, Riederer P, Gerlach M. Dopaminergic dysbalance in distinct basal ganglia neurocircuits: implications for the pathophysiology of Parkinson's disease, schizophrenia and attention deficit hyperactivity disorder. Neurotox Res 2006;10:167-179.

Mellick GD, Silburn PA, Sutherland GT, Siebert GA. Exploiting the potential of molecular profiling in Parkinson's disease: current practice and future probabilities. Expert Rev Mol Diagn 2010;10:1035-1050.

Menza M. The personality associated with Parkinson's disease. Curr Psychiatry Rep 2000;2:421-426.

Merims D, Giladi N (2008). "Dopamine dysregulation syndrome, addiction and behavioral changes in Parkinson's disease". Parkinsonism Relat Disord 2008;14:273–280.

Mok W, Chow TW, Zheng L, Mack WJ, Miller C. Clinicopathological concordance of dementia diagnoses by community versus tertiary care clinicians. Am J Alzheimers Dis Other Dement 2004;19:161-165.

Moody TD, Bookheimer SY, Vanek Z, Knowlton BJ. An implicit learning task activates medial temporal lobe in patients with Parkinson's disease. Behav Neurosci 2004;118:438-442.

Moretti R, Torre P, Rodolfo MA, Giuseppe C, Bava, A. Ten-point clock test: A correlation analysis with other neuropsychological tests in dementia. Int J Ger Psychiat 2002;17:347–353.

Mountjoy CQ, Roth M. Studies in the relationship between depressive disorders and anxiety states. Part 1. Rating scales. J Affect Disord 1982; 4: 127-147.

Mueller SG, Schuff N, Yaffe K, Madison C, Miller B, Weiner MW. Hippocampal atrophy patterns in mild cognitive impairment and Alzheimer's disease. Hum Brain Mapp 2010;31:1339-1347.

Myers CE, Kluger A, Golomb J, Ferris S, de Leon MJ, Schnirman G, Gluck MA. Hippocampal atrophy disrupts transfer generalization in nondemented elderly. J Ger Psychiat Neurol 2002;15:82-90.

Myers CE, Shohamy D, Gluck MA, Grossman S, Kluger A, Ferris S, Golomb J, Schnirman G, Schwartz R. (2003). Dissociating hippocampal versus basal ganglia contributions to learning and transfer. J Cogn Neurosci 2003;15:185-193.

Nagy H, Kéri S, Myers CE, Benedek G, Shohamy D, Gluck MA. Cognitive sequence learning in Parkinson's disease and amnestic mild cognitive impairment: Dissociation between sequential and non-sequential learning of associations. Neuropsychologia 2007;45:1386-1392.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology. 1998 Dec;51(6):1546-54. Review.

Nelissen N, Vandenbulcke M, Fannes K, Verbruggen A, Peeters R, Dupont P, Van Laere K, Bormans G, Vandenberghe R. Abeta amyloid deposition in the language system and how the brain responds. Brain 2007;130:2055-2069.

Nickl-Jockschat T, Kleiman A, Schulz JB, Schneider F, Laird AR, Fox PT, Eickhoff SB, Reetz K. Neuroanatomic changes and their association with cognitive decline in mild cognitive impairment: a meta-analysis. Brain Struct Funct 2011 Jun 12. [Epub ahead of print]

Pachana NA, Boone KB, Miller BL, Cummings JL, Berman N. Comparison of neuropsychological functioning in Alzheimer's disease and frontotemporal dementia. J Int Neuropsychol Soc 1996;2:505–510.

Parasuraman R, Greenwood PM, Alexander GE. Alzheimer disease constricts the dynamic range of spatial attention in visual search. Neuropsychologia 2000;38:1126-1135.

Perez-Lloret S, Rascol O. Dopamine receptor agonists for the treatment of early or advanced Parkinson's disease. CNS Drugs 2010;24:941-968.

Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 2006;442:1042-1045.

Pinto E, Peters R. Literature review of the Clock Drawing Test as a tool for cognitive screening. Dement Geriatr Cogn Disord 2009;27:201-213.

Poldrack RA, Clark J, Paré-Blagoev EJ, Shohamy D, Creso Moyano J, Myers C, Gluck MA. Interactive memory systems in the human brain. Nature 2001;414:546-550.

Rascovsky K, Salmon DP, Ho GJ, Galasko D, Peavy GM, Hansen LA, Thal LJ. Cognitive profiles differ in autopsy-confirmed frontotemporal dementia and AD. Neurology 2002;58:1801–1808.

Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry. 1982 Sep;139(9):1136-9.

Rouleau I, Salmon DP, Butters N, Kennedy C, McGuire K. Quantitative and qualitative analyses of clock drawings in Alzheimer's and Huntington's disease. Brain Cogn 1992;18:70–87.

Royall DR, Cordes JA, Polk M. CLOX: An executive clock drawing task. J Neurol Neurosurg Psychiatry 1998;64:588–594.

Rózsa S, Kállai J, Osváth A, Bánki MC. Temperamentum és Karakter: Cloninger pszichobiológiai modellje. A Cloninger-féle Temperamentum és Karakter Kérdőív felhasználói kézikönyve. Medicina: Budapest, 2005.

Saint-Cyr JA, Taylor AE, Lang AE. Procedural learning and neostriatal dysfunction in man. Brain 1988;111:941-959.

Santesso DL, Evins AE, Frank MJ, Schetter EC, Bogdan R, Pizzagalli DA. Single dose of a dopamine agonist impairs reinforcement learning in humans: evidence from event-related potentials and computational modeling of striatal-cortical function. Hum Brain Mapp 2009;30:1963-1976.

Schmidtke K, Olbrich S. The Clock Reading Test: validation of an instrument for the diagnosis of dementia and disorders of visuo-spatial cognition. Int Psychogeriatr 2007;19:307-321.

Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. Lancet Neurol 2006;5:355-363.

Schultz W. Multiple dopamine functions at different time courses. Annu Rev Neurosci 2007;30:259-288.

Schroeter ML, Stein T, Maslowski N, Neumann J. Neural correlates of Alzheimer's disease and mild cognitive impairment: a systematic and quantitative meta-analysis involving 1351 patients. Neuroimage 2009;47:1196-1206.

Selikhova M, Williams DR, Kempster PA, Holton JL, Revesz T, Lees AJ. A clinico-pathological study of subtypes in Parkinson's disease. Brain 2009;132:2947-2957.

Shohamy D, Myers CE, Geghman KD, Sage J, Gluck MA. L-dopa impairs learning, but spares generalization, in Parkinson's disease. Neuropsychologia 2006;44:774-784.

Shulman KI. Clock-drawing: Is it the ideal cognitive screening test? Int J Geriat Psychiatry 2000;15:548–561.

Siegert RJ, Taylor KD, Weatherall M, Abernethy DA. Is implicit sequence learning impaired in Parkinson's disease? A meta-analysis. Neuropsychology 2006;20:490-495.

Smith KS, Berridge KC, Aldridge JW. Disentangling pleasure from incentive salience and learning signals in brain reward circuitry. Proc Natl Acad Sci USA 2011;108:E255-264.

Spencer AH, Rickards H, Fasano A, Cavanna AE. The prevalence and clinical characteristics of punding in Parkinson's disease. Mov Disord 2011;26:578-586.

Sperling R. Functional MRI studies of associative encoding in normal aging, mild cognitive impairment, and Alzheimer's disease. Ann NY Acad Sci 2007;1097:146-155.

Tomer R, Aharon-Peretz J. Novelty seeking and harm avoidance in Parkinson's disease: effects of asymmetric dopamine deficiency. J Neurol Neurosurg Psychiatry 2004;75:972-975.

Tosun D, Schuff N, Mathis CA, Jagust W, Weiner MW; Alzheimer's Disease NeuroImaging Initiative. Spatial patterns of brain amyloid-beta burden and atrophy rate associations in mild cognitive impairment. Brain 2011;134:1077-1088.

Tranel D, Rudrauf D, Vianna EP, Damasio H. Does the Clock Drawing Test have focal neuroanatomical correlates? Neuropsychology 2008;22:553-562.

Tuokko H, Hadjistavropoulos T, Miller JA, Beattie BL. The Clock Test: a sensitive measure to differentiate normal elderly from those with Alzheimer disease. J Am Geriatr Soc 1992;40:579-584.

Vandenberghe R, Price C, Wise R, Josephs O, Frackowiak RS. Functional anatomy of a common semantic system for words and pictures. Nature 1996;383:254-256.

van Halteren-van Tilborg IA, Scherder EJ, Hulstijn W. Motor-skill learning in Alzheimer's disease: a review with an eye to the clinical practice. Neuropsychol Rev 2007;17:203-212.

van Tilborg I, Hulstijn W. Implicit motor learning in patients with Parkinson's and Alzheimer's disease: differences in learning abilities? Motor Control 2010;14:344-361.

Venda LL, Cragg SJ, Buchman VL, Wade-Martins R. α-Synuclein and dopamine at the crossroads of Parkinson's disease. Trends Neurosci 2010;33:559-568.

Vitale C, Santangelo G, Trojano L, Verde F, Rocco M, Grossi D, Barone P. Comparative neuropsychological profile of pathological gambling, hypersexuality, and compulsive eating in Parkinson's disease. Mov Disord 2011;26:830-836.

Voon V, Sohr M, Lang AE, Potenza MN, Siderowf AD, Whetteckey J, Weintraub D, Wunderlich GR, Stacy M. Impulse control disorders in Parkinson disease: a multicenter case-control study. Ann Neurol 2011a;69:986-996.

Voon V, Gao J, Brezing C, Symmonds M, Ekanayake V, Fernandez H, Dolan RJ, Hallett M. Dopamine agonists and risk: impulse control disorders in Parkinson's disease Brain. 2011b;134:1438-1446.

Wechsler D. Wechsler Adult Intelligence Scale - Revised Manual. Psychological Corporation: New York, NY, 1981.

Wilkinson L, Lagnado DA, Quallo M, Jahanshahi M. The effect of feedback on non-motor probabilistic classification learning in Parkinson's disease. Neuropsychologia. 2008;46:2683-2695.

Woodward M, Brodaty H, Boundy K, Ames D, Blanch G, Balshaw R; PRIME Study Group. Does executive impairment define a frontal variant of Alzheimer's disease? Int Psychogeriatr 2010;22:1280-1290.

Yahr MD, Duvoisin RC, Schear MJ, Barrett RE, Hoehn MM. Treatment of parkinsonism with levodopa. Arch Neurol 1969;21:343–354.

Yin HH, Knowlton BJ. The role of the basal ganglia in habit formation. Nat Rev Neurosci 2006;7:464-476.

Zald DH, Cowan RL, Riccardi P, Baldwin RM, Ansari MS, Li R, Shelby ES, Smith CE, McHugo M, Kessler RM. Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. J Neurosci 2008;28:14372-14378.

9. List of own publications related to the thesis

1: Bódi N, Kéri S, Nagy H, Moustafa A, Myers CE, Daw N, Dibó G, Takáts A, Bereczki D, Gluck MA. (2009) Reward-learning and the novelty-seeking personality: a between- and within-subjects study of the effects of dopamine agonists on young Parkinson's patients. Brain. 132(Pt 9):2385-95.

2: Bódi N, Csibri E, Myers CE, Gluck MA, Kéri S. (2009) Associative learning, acquired equivalence, and flexible generalization of knowledge in mild Alzheimer disease. Cogn Behav Neurol. 22(2):89-94.

3: Blair M, Kertesz A, McMonagle P, Davidson W, Bodi N. (2006) Quantitative and qualitative analyses of clock drawing in frontotemporal dementia and Alzheimer's disease. J Int Neuropsychol Soc. 12(2):159-65.

10. List of own publications independent of the thesis

1: Seres I, Unoka Z, *Bódi N*, Aspán N, Kéri S. (2009) The neuropsychology of borderline personality disorder: relationship with clinical dimensions and comparison with other personality disorders. J Pers Disord. 23(6):555-62.

2: Unoka Z, Seres I, Aspán N, *Bódi N*, Kéri S. (2009) Trust game reveals restricted interpersonal transactions in patients with borderline personality disorder. J Pers Disord. 23(4):399-409.

3: Vincze G, Almos P, Boda K, Döme P, *Bódi N*, Szlávik G, Maglóczki E, Pákáski M, Janka Z, Kálmán J. (2007) Risk factors of cognitive decline in residential care in Hungary. Int J Geriatr Psychiatry. 22(12):1208-16.

4: Must A, Szabó Z, *Bódi N*, Szász A, Janka Z, Kéri S. (2005) Neuropsychological assessment of the prefrontal cortex in major depressive disorder. Psychiatr Hung. 20(6):412-6. Hungarian.

5: Must A, Szabó Z, *Bódi N*, Szász A, Janka Z, Kéri S. (2006) Sensitivity to reward and punishment and the prefrontal cortex in major depression. J Affect Disord. 90(2-3):209-15.

6: Juhász A, Rimanóczy A, Boda K, Vincze G, Szlávik G, Zana M, Bjelik A, Pákáski M, *Bódi N*, Palotás A, Janka Z, Kálmán J. (2005) CYP46 T/C polymorphism is not associated with Alzheimer's dementia in a population from Hungary. Neurochem Res. 30(8):943-8.

7: Galariotis V, *Bódi N*, Janka Z, Kálmán J. (2005) Frontotemporal dementia--part III. Clinical diagnosis and treatment. Ideggyogy Sz. 58(9-10):292-7. Review.

8: Juhász A, Palotás A, Janka Z, Rimanóczy A, Palotás M, *Bódi N*, Boda K, Zana M, Vincze G, Kálmán J. (2005) ApoE -491A/T promoter polymorphism is not an independent risk factor, but associated with the epsilon4 allele in Hungarian Alzheimer's dementia population. Neurochem Res. 30(5):591-6.

9: Galariotis V, *Bódi N*, Janka Z, Kálmán J. (2005) Frontotemporal dementia--Part II. Differential diagnosis, genetics, molecular pathomechanism and pathology. Ideggyogy Sz. 58(7-8):220-4. Review.

10: Galariotis V, *Bódi N*, Janka Z, Kálmán J. (2005) Frontotemporal dementia--Part I. History, prevalence, clinical forms. Ideggyogy Sz. 58(5-6):164-71. Review.

11: Fehér LZ, Kálmán J, Puskás LG, Gyülvészi G, Kitajka K, Penke B, Palotás M,Samarova EI, Molnár J, Zvara A, Matin K, *Bódi N*, Hugyecz M, Pákáski M, Bjelik A, Juhász A, Bogáts G, Janka Z, Palotás A. (2005) Impact of haloperidol and risperidone on gene expression profile in the rat cortex. Neurochem Int. 47(4):271-80. PubMed PMID: 15941608.

12: Kálmán J, Palotás A, *Bódi N*, Kincses TZ, Benedek G, Janka Z, Antal A. (2005) Lactate infusion fails to improve semantic categorization in Alzheimer's disease. Brain Res Bull. 65(6):533-9.

13: *Bódi N*, Hegedűs Z, Rudas L, Zöllei É, Csanády M, Csanádi Z: (2004) **"**Twiddler's- szindróma" implantábilis cardioverter defibrillator beültetés után. Card Hung. 34:201-204.

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