FEELING OF KNOWING, VERB PROCESSING AND EXECUTIVE FUNCTIONS IN NON-DEMENTED PARKINSON'S DISEASE PATIENTS

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Thesis Abstract

Bengi Baran, "Feeling-of-Knowing, Verb Processing and Executive Functions in Non-Demented Parkinson's Disease Patients"

The aim of this present study was to explore whether feeling-of-knowing (FOK) judgments are related with executive functioning of the frontal lobes in non-demented Parkinson's Disease (PD) patients and to compare noun versus verb processing at three different levels (memory, metamemory and word generation). It was predicted that PD patients would be impaired in episodic memory and metamemory and they would perform worse for verb targets than nouns. An episodic task of paired associate learning for 32 word pairs was used in this study. It was found that PD patients were impaired in recall and recognition as compared to controls. Only the PD group performed worse on verb recognition implying an episodic memory deficit for verbs as a lexical category. Accuracy of FOK judgments was not above the chance level implying that metamemory monitoring is significantly impaired in this patient population. To explore the relationship between FOK accuracy and executive functions, two tests of executive functioning were used: Verbal fluency (semantic, lexical and action fluency) and Wisconsin Card Sorting Test (WCST). PD patients were impaired in all tests of verbal fluency but magnitude of difference was greater for the action fluency test which supports existing literature that verb generation tasks are especially sensitive to PD related cognitive changes. For the PD group neither WCST nor verbal fluency composite scores significantly correlated with FOK accuracy measures. However for healthy controls, WCST performance is a strong predictor of FOK accuracy.

Tez Özeti

Bengi Baran, "Demansız Parkinson Hastalarında Bilme Hissi,

Fiil İşlemleme ve Yürütücü İşlevler"

Bu çalışmanın amacı demanssız Parkinson hastalarında (PH) bilme hissi yargılarının frontal lobların yürütücü işlevleri ile ilişkili olup olmadığını araştırmak ve isim-fill işlemlemeyi üç farklı seviyede (bellek, metabellek ve kelime türetme) karşılaştırmaktır. PH grubunun episodik bellek ve matabellek performanslarının bozuk olacağı ve isim hedefler ile kıyaslandığında fiil hedefler için daha kötü performans gösterecekleri öngörülmüştür. Bu çalışmada bir episodik ödev olan 32 kelimelik çiftli ilişki öğrenme testi kullanılmıştır. PH grubunun geri getirme ve tanımalarının kontrollere kıyasla bozuk olduğu bulunmuştur. Sadece PH grubunda fiil tanıma daha bozuktur, ki bu da bir leksikal kategori olarak fiiller için episodik bellek bozuklukları olduğunu düşündürmektedir. Bilme hissi yargılarının doğruluğu şans düzeyinin üstünde değildi, ki bu da metabellek monitor edebilme becerisinin bu hasta populasyonunda anlamlı bir şekilde bozulduğunu göstermektedir. Bilme hissi yargıları ve yürütücü işlevler arasındaki ilişkinin araştırılması için iki yürütücü işlev testi kullanılmıştır: sözel akıcılık (semantik akıcılık, leksikal akıcılık ve eylem akıcılığı) ve Wisconsin Kart Eşleme Testi (WKET). PH grubu tüm sözel akılcık testlerinde bozukluk gösterirken bu bozukluğun şiddeti eylem akıcılığı için daha fazlaydı, ki bu bulgu eylem türetme testlerinin PH'ye ilişkin kognitif bozulmalara daha hassas olduğu hakkında varolan literatürü desteklemektedir. PH grubu için WKET ya da sözel akıcılık bileşik skorları bilme hissi doğruluk ölçütleri ile anlamlı bir korelasyon göstermemiştir. Ancak sağlıklı kontroller için, WKET performansı bilme hissi doğruluğunu güçlü bir şekilde açıklamaktadır.

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CHAPTER 1: INTRODUCTION

Parkinson's Disease and Cognitive Impairment

Parkinson's disease (PD) is a progressive neurodegenerative disorder associated with fundamental motor symptoms like resting tremor, rigidity of the limbs, slowness of movements and reflexes (bradykinesia) and postural instability (Tolosa, Wenning & Poewe, 2006). A diagnosis of PD is made when at least two of these four motor symptoms are present and especially when motor complaints start asymmetrically on one side of the body. Although initially described by James Parkinson in 1817 as a motor disturbance (paralysis agitans) in which intellectual abilities and senses were intact, now it is widely accepted that changes in cognition accompany the disease. Specifically, cognitive changes in PD are being more and more recognized as a part of the disease process itself. However, there is no single profile of cognitive impairment or course of progress seen uniformly in all PD patients (Pillon, Boller, Levy & Dubois, 2001). Therefore, a consensus is not yet established and there is ample need for more research and strong empirical evidence.

In terms of epidemiology, average disease onset is 60 years of age with a prevalence of 3 per 1000 persons over the entire population and about 1% among people over 65 years of age (Nussbaum & Ellis, 2003). There is also an early onset form (before the age of 40) and a juvenile subtype (before the age of 21) which is very rare and in most of the cases familial (Lonneke & Breteler, 2006).

As reviewed by Emre (2004), various researchers agree that a particular type of dementia is associated with PD (Parkinson's disease dementia- PDD) which typically consists of impairments of executive functions, visuo-spatial functions and attention related secondary impairments in learning and memory. Not all PD patients are eventually demented and longitudinal evidence suggests that 4 years after the initial onset, 25% of PD patients develop PDD (Aarsland et al., 2001 cited in Kertesz, 2003). However, risk factors that contribute to conversion from PD to PDD are not yet established and the only robust feature that separates the two groups is the significantly shorter survival rate in PDD populations (Pillon et al., 2001). PDD significantly overlaps with other dementing conditions like Alzheimer's disease in terms of pathology as well as biochemical and clinical underpinnings (Kertesz, 2003).

Underlying pathophysiological changes in PD include neuronal loss in the substantia nigra of the basal ganglia which is the main site of dopamine production; catecholaminergic and cholinergic neurons ascending from the brainstem may further be degenerated thus exacerbating cognitive deficits (Pillon et al., 2001) There is not one specific type of atrophy to diagnose PD. High-field MRI, a specific imaging technique, shows signal changes in substantia nigra; however a specific MRI marker is not yet available and diagnosis of PD is made primarily by clinical observation (Tolosa, Wenning & Poewe, 2006).

In terms of cognitive impairment, PD is evidenced to disturb executive functions, memory, visuospatial functioning and speech (Pillon et al., 2001). Lesions of the frontal lobes interfere with executive functioning, which broadly consist of establishing goals, planning and sequencing, abstract thinking, perseverance and overcoming interference (e.g. Chudasama & Robbins, 2006). Impairment of executive functions can also be seen following damage to structures of the fronto-striatal network like the basal ganglia (Chudusama & Robbins, 2006). Thus, executive deficits observed in PD patients have been suggested to emerge from abnormalities in cortico-striatal-thalamo-cortical loops (Taylor & Saint-Cyr, 1995). These cortico-striatal loops involve parallel processing of descending cortical information which is projected to the striatum and pallidum of the basal ganglia, then to the thalamic nuclei from where they are relayed back to the cortex (Chudusama & Robbins, 2006). Hence, PD is associated with decreased levels of dopamine not only in the striatum but also in the frontal lobes; and parts of the caudate nucleus that project to the dorsolateral prefrontal cortex are especially involved in this dopaminergic degeneration process (Higginson et al., 2003). An issue of debate is whether the executive deficits observed in PD derive from pathophysiological changes in the prefrontal cortex, basal ganglia or the striatum in particular, or from the disruption of the connections between these two structures (Dirnberger, Frith & Jahanshahi, 2005) and a definitive consensus has not been reached yet. Accordingly, it is suggested that executive deficits observed in PD are different from those of patients with frontal damage; PD patients are specifically impaired when they have to conceptualize a set of rules or have to engage in set shifting (Pillon et al., 2001) but unlike patients with frontal damage they exhibit less perseverations (Rippon & Marder, 2005).

To measure the nature and extent of executive deficits in PD, Owen et al. (1992) compared medicated (with 15 mild to moderate versus 14 severe PD patients) and non-medicated PD (13 in stages I and II; 2 in stage III) patients with matched controls using a computerized version of the Tower of London test which measures planning, set shifting and visuo-spatial attention. Non-medicated PD patients did not differ from the controls in terms of overall accuracy rates and initiation times but medicated patients were impaired in the amount of time they spent thinking about the solution to each problem compared to non-medicated or control groups. However, all PD groups were significantly impaired in attentional set shifting and formulating and maintaining correct response patterns. Of particular note in this study is that, a majority of the non-medicated group (13 out of 15 patients) had milder PD (Hoehn-Yahr stages I-II) whereas the medicated group had a more even distribution of disease severity (15 patients with mild-moderate, 14 patients with severe PD).

Memory impairment in PD is qualitatively different from other degenerative disorders like Alzheimer's disease (AD) in that PD patients perform worse on recall tests but are usually comparable with controls on recognition tests, implying that their complaints of forgetfulness is secondary to deficits in attention and working memory, whereas AD patients are impaired in both (Nussbaum & Ellis, 2003). This reflects the underlying neuropathology, AD presents with neuronal loss in medial temporal regions (e.g. Mesulam, 2000). Conversely, the hippocampal or encoding component of memory is preserved but working memory (WM) which depends on dorsolateral prefrontal cortical activation is impaired in PD (Pillon et al., 2001). Performance on tests of WM is highly correlated with recall performance and WM scores statistically predict and explain variance in the recall performance of PD patients, an effect which is significantly less strong in normal populations (Higginson et al., 2003).

Metamemory in Parkinson's Disease

Of primary interest in this study is metamemory in PD and its relationship with executive functioning. Metamemory refers to self-directed processes between decision-making and memory. In other words, it is the individual's knowledge and monitoring on each stage of acquisition, retention and retrieval of items (Nelson & Narens, 1994). Metacognitive processes by definition require a modifying and controlling model over cognitive functioning.

In their framework on metamemory, Nelson and Narens (1994) termed two interrelated levels of cognition as "meta-level" and "object-level". An example of an object level process could be recalling a particular information, whereas a meta level process would be reporting whether that information could be recalled or not at that moment. The flow of information from meta to object level essentially modifies the object level towards actualization or termination of an action. On the other hand, the flow of information from object to meta level is via monitoring. More precisely, the object level gives situational information to the meta-level but cannot modify it.

Memory monitoring processes may be discriminated on the temporal basis: prospective versus retrospective monitoring (Nelson & Narens, 1994). Retrospective judgments typically involve confidence judgments in which the subjects rate their degree of confidence in a previous recall or recognition response. Prospective judgments can be made prior to the learning phase to decide whether it would be easy to learn the item (Ease-of-learning judgments), during the learning phase to predict future recall or recognition of currently recallable items (Judgments-of-learning), or after the learning phase to determine whether currently nonrecallable items will be recognized in the future (Feeling-of-knowing judgments). The type of memory monitoring process that is within the main scope of this proposal is feeling-of-knowing (FOK). Research on FOK judgments are derived from the fact that memory is fallible and thus, when an individual fails to retrieve an item, a monitoring process of storage states for that item becomes essential (Hart,1967). FOK is a person's judgment on whether an item that currently cannot be recalled will be retrieved or recognized in the future (Nelson & Narens, 1994). In a typical procedure, subjects are given a recall test and are asked to give FOK ratings for those questions that they are unable to answer. A FOK state is usually defined as the feeling that the person knows the answer and that he can identify the correct answer among other choices in a subsequent recognition test. Then subjects are given a recognition test for those questions.

Two main concepts about FOK judgments have been of interest in terms of analysis. The first is the strength of FOK judgments (i.e. how high do subjects rate their FOK). The second concept of interest is the predictive accuracy of FOK judgments (i.e. is the subject's subsequent recognition performance in line with his/her FOK ratings).

Metamemory processes have been studied in several patient populations; for instance, in patients with Alzheimer's disease, FOK accuracy was close to zero and patients made significantly more misses and less hits for items that they initially gave a positive FOK judgment as compared to young and older control groups (Souchay, Isingri & Gil, 2002).

Another study investigated FOK judgments in patients with focal frontal lobe lesions (Schnyer et al., 2004). Subjects learned sentences and subsequently were asked to recall the last word of each sentence. The authors showed that lesions in the right medial prefrontal cortex were associated with the worst metamemory accuracy.

In a recent fMRI study of encoding and retrieval of paired associate learning, subjects first studied word pairs and were then given a cue word and decided whether they knew the target (“know”), could not recall the target but would recognize it among a list of distractors (“FOK”), or could not recall or recognize the target (“don’t know”). (Maril et al., 2003). Analysis of the imaging data revealed activation in the left inferior frontal gyrus and left middle frontal cortex in FOK trials; implying that the frontal network plays a pivotal role in this partial or graded recall phenomenon.

With regard to PD, there are very few studies on metacognitive judgments. This lack of empirical evidence is surprising since the fronto-striatal degeneration in PD, which may interfere with retrieval strategies, is an ideal model to study memory monitoring and control processes.

Although not directly measuring FOK, Johnson and colleagues (2005) attempted to explore metamemory deficits in PD patients. The researchers used the Metamemory in Adulthood (MIA) questionnaire (Dixon & Hultsch, 1983 cited in Johnson et al., 2005) which is a self administered questionnaire with seven metamemory dimensions of capacity, change, task, strategy, anxiety, achievement and locus. PD patients reported less memory efficacy, less use of external strategies such as making to-do lists or asking for caregiver prompting. However in their sample, PD patients were significantly older than the controls. Also, efficient self evaluation of memory capacity requires intact insight and self monitoring, which may not be intact in this patient population.

In an early empirical study, FOK judgments for semantic knowledge was compared between depressed versus non-depressed PD patients and age matched controls (Coulter, 1989); accuracy of FOK was similar across control and PD groups and depression did not lead to any significant differences. Similarly, in a more recent study of verbal memory in PD patients without dementia, FOK judgments for semantic knowledge did not differ in strength or accuracy between patients and matched controls (Ivory et al., 1999).

Both of these studies dealt with the monitoring of semantic knowledge in PD patients. However, Janowski, Shimamura & Squire (1989) have shown that among patients with damage to frontal lobes, accuracy of semantic FOK is spared whereas episodic FOK is impaired. As a further support to this finding, Souchay, Isingrini & Espagnet (2000) have shown that in a sample of healthy aged subjects and young controls, only episodic FOK is significantly correlated with tests of executive functioning and thus frontal networks have to be intact in order for episodic FOK judgments to be accurate.

With a sample of PD patients and age matched healthy controls, Souchay, Isingri & Gil (2006) have used 20 word pairs and asked subjects to make two metamemory judgments: global predictions (how many of these 20 word pairs would the subjects be able to recall) and item based judgments (i.e. FOK- for those target words not recalled after seeing the cue word; would subjects be able to recognize the word among distractors). In terms of the strength of FOK judgments no significant difference was observed. PD group's accuracy for global predictions was comparable to that of the control group and both groups predicted recalling less items than they were actually able to recall. FOK accuracy, on the other hand, was significantly lower for PD patients. However, in this study, the researchers did not use any measure of executive functioning to support their hypothesis that executive functions are impaired in PD patients and episodic metamemory is dependent upon executive abilities and frontal lobe functioning whereas semantic metamemory is not.

Another question addressed in this study was whether dissociation between noun and verb processing could be observed with PD related cognitive changes. Differential processing of nouns and verbs has long been an issue of interest for neural scientists. Lesion studies have shown that actions or verbs are retrieved via different neural networks. For instance, Damasio and Tranel (1993) have obtained neuropsychological data from three patients: Boswell has severe retrograde and anterograde amnesia due to herpes simplex encephalitis which resulted in bilateral destruction of the mesial temporal structures (that include amygdala, hippocampus and the entorhinal cortex) and bilateral atrophy in insular and orbitofrontal cortices. Boswell has impaired concept and lexical retrieval. Patient AN-1033 had a lesion in the left anterior temporal lobe which resulted in impairments in lexical retrieval whereas conceptual retrieval remained intact. Finally, patient KJ-1360 had a left premotor lesion and fully recovered from a transcortical motor aphasia and at present had intact concept retrieval but selective lexical impairment. They compared the performances of these patients with normal controls in three different retrieval tests: noun retrieval (confrontation naming of pictures of animals, fruits/vegetables and tools/utensils), proper noun retrieval (personally significant faces and famous public faces), and verb retrieval. They found that Boswell and AN-1033 were markedly impaired in proper name and noun retrieval tasks and were more impaired in animals and fruits/vegetables than tools but performed similar to controls in the verb retrieval task. However, KJ-1360 had the opposite profile with relatively preserved retrieval of nouns and proper names (he was within two SDs of the mean scores of controls) but severely impaired verb retrieval.

Damasio and Tranel (1993) discuss that neural networks essential for the retrieval of proper and common nouns are in the left anterior and middle temporal cortices and damage to these areas spares verb naming whereas systems essential for verb retrieval are in the left frontal cortex. However, as they caution, this dissociation is not to be applied to verb or noun processing as a whole and such lesions do not lead to total loss of representations of nouns or verbs and that "word forms may still be reactivated from their highly distributed and fragmentary base representations in auditory, kinesthetic and motor cortices" (p. 4959). In this respect, they imply that word forms do not have certain permanent stores but interacting neural networks with feed-forward and feed-back connections that act as mediators between concepts and word forms. Thus, this lesion study predicts a dissociation between neural circuitry that mediate access to nouns which are in close anatomical proximity of concrete entities in the anterior and middle temporal cortex; and neural structures that mediate access to verbs which are in close anatomical proximity of concepts of movement and space-time relations in frontal cortical areas.

More recently, Tranel and colleagues (2005) have investigated the differential processing of word class ambiguous verbs and nouns (i.e. noun-verb homonyms). The authors have observed a striking example about this class of words: when a severely anomic patient was shown a picture of a comb, he replied ''I can't think of the name of that; I know that you use it to comb your hair, but I don't remember the name.'' (p.289). In their study, Tranel et al. (2005) used PET to explore neural substrates of homonymous noun/verb processing. Subjects were presented with pictures of four types of stimuli: tools that are named with non-homonymous nouns (e.g. *camera*), tools that are named with homonymous nouns (e.g. *comb*), actions that are named with non-homonymous verbs (e.g. *juggle*) and, actions that are named with homonymous verbs (e.g. *to drill*). Each participant was shown the picture and was asked to name it while undergoing PET.

In line with their hypotheses, the authors found that naming tools lead to activations in the left posterior ventral inferotemporal (IT) region and naming actions lead to activations in the left frontal opercular (FO) and left middle temporal (MT). Contrasting homonymous and non-homonymous nouns did not result in any significant differences, however when examined separately homonymous nouns activated both the above mentioned noun area and part of the verb area. Similarly, subtraction of homonymous from non-homonymous verbs was not significant, but activation of the verb area was weaker for homonymous verbs. Also when compared with nouns, verbs yielded more left MT activation but verbs also caused posterior IT ("noun" area) activation which led the authors to suggest that the verb pattern was not completely dissociable from the noun pattern.

Shapiro, Moo and Caramazza (2006) argue that functional imaging during confrontation naming with pictures has its limitations in that performance is related to visual recognition. The authors used a more grammatical task in which subjects produced verbs or nouns within the context of a phrase or short sentence (e.g. *many doors, he weeps*) while they underwent fMRI. They found two specific activation patterns associated with noun versus verb production: when producing verbs the left prefrontal cortex, left superior parietal lobule and left superior temporal gyrus showed significantly more activation whereas with nouns the left anterior fusiform gyrus was more active. The authors speculate that the reason for this anterior fusiform activation in noun production may be due to its "proximity to posterior fusiform regions involved in object recognition and classification" (p. 1647). Similarly, of the three areas activated specifically with verb production, the left prefrontal areas involve representations of motor schemata and left parietal areas are involved in motor or spatial attention and body image representations of action postures (Shapiro, Moo & Caramazza, 2006).

Moving on from the notion that neural networks for language, action and perception are quite interconnected, Hauk, Johnsrude and Pulvermüller (2004) have attempted to explore possible relationships between verb processing and motor areas. They suggest that if nouns are closely associated with their visual images, then activity related with their comprehension may be found in temporal visual areas. Similarly, action words related with body movements would activate frontocentral motor areas. They tested the latter hypothesis with a passive reading task of 3 categories of action words (leg, arm and face related verbs) while subjects underwent fMRI. They found that actions regarding arms, legs or the face activated related primary motor and premotor areas. This robust finding has prompted the authors to conclude that action words and the perceptions related to them are processed together and are represented within the same broad neural network.

Related with this issue of interconnectivity, Bak and colleagues (2006) describe a family with a progressive movement disorder (which resembles progressive supranuclear palsy- PSP) and dementia which selectively impaired verb processing. The father was a 69 year old man with an 18 month history of mental slowing, forgetfulness, gait disturbance and falls. He was impaired in tests of executive abilities, attention, verbal and visual memory, visuospatial functioning, naming, repetition and comprehension. His deficit in naming was significantly more pronounced for verbs than nouns and this difference remained stable in the 2 year follow-up. In the terminal stages of deterioration he became mute and developed dysphagia and dysartria and had severe limitation of vertical saccades. His son, then aged 42 years, presented similar cognitive and motor symptoms and vertical gaze palsy. His neuropsychological profile was similar to his father but less severe. Also progression was slower in his case. He too had marked difficulty with verb naming. The authors provided longitudinal evidence for this dissociation with several tests of naming, comprehension, picture association and lexical decision. In terms of neuroanatomical correlates of these impairments, areas revealing most significant atrophy involved the frontal poles and inferior regions of the frontal cortex which extended to the temporal poles whereas the basal ganglia were mildly atrophied. This selective impairment in verb processing, as the authors put forward, provides further evidence for the interconnectivity of movement and language; specifically verb processing and motor areas and suggests a possible genetic factor associated with both systems.

Action and object naming performances have been compared across patients with different dementing disorders like Alzheimer's Disease (AD), frontotemporal dementia (FTD), semantic dementia (SD), corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP) (Cotelli et al., 2006). The researchers have found that FTD, PSP, CBD and AD patients were more impaired in action than object naming compared to the control subjects and the SD patients with but this discrepancy was smaller in the AD group.

In a related further study by the same research team, when a group of early PD patients were compared with age matched controls, they performed similarly on the object naming test but PD patients performed significantly worse on action naming (Cotelli et al., 2007).

Related to this word class difference between verbs and nouns is the semantic distinction of manipulability (whether an object or action requires fine hand movements). The hypothesis behind the neuroanatomical quest of this semantic distinction is that “the way we act on objects has an impact on how the information about those objects is represented and retrieved”, for instance cortical areas devoted to grasping a pair of scissors may become part of the mental representation of that object (Saccuman et al., 2006). In a recent fMRI study, subjects were asked to name: a) manipulable nouns (e.g. key), b) non manipulable nouns (e.g. airplane), c) manipulable verbs (e.g. squeeze), and d) non manipulable verbs (e.g. walk). The authors have shown that manipulability modulated the pattern of brain activation (with manipulable verbs and nouns activating fronto-parietal regions) whereas word class differences did not yield to significant differences in activation (Saccuman et al., 2006). However, within a sample of PD patients, Cotelli and colleagues (2007) did not find any difference in the naming of manipulable versus non-manipulable verbs.

Piatt and colleagues (1999) compared verbal fluency performances of cognitively intact PD patients with PD patients who scored below age-appropriate averages in at least two of four main cognitive domains (language, memory, executive function and visuospatial function) and labeled this group as PDD patients (Parkinson’s disease with Dementia). Subjects were given lexical fluency (saying as many words as they can in one minute starting with the letters F, A and S), semantic fluency (words from the category of animals) and action fluency tests (generating as many actions as possible in one minute). They found that PDD patients were more impaired in all three tasks than PD patients and controls, but this difference was greater in magnitude for action fluency. However, in their sample cognitively intact PD patients performed quite similarly with age and education matched controls. A problem with this study is that they do not provide any diagnostic criteria to distinguish mild or early cognitive impairment in PD from dementia of Parkinson's disease. Given that incidence of dementia is not frequent among PD patients, labeling patients who score below average on two or more cognitive domains as demented is disputable. Nevertheless, this study provides ample evidence that cognitive impairment associated with PD selectively involves verb processing.

To further explore the nature and extent of this verb production deficit, Péran and colleagues (2003) have designed a verb generation task in which non-demented PD patients and matched controls were given a noun or verb and were asked to generate a semantically related noun or verb. The study consisted of two intracategory tasks: hearing a noun and producing a noun (N-N), hearing a verb and producing a verb (V-V); and two intercategory tasks: hearing a noun and producing a verb (N-V), hearing a verb and producing a noun (V-N). PD patients performed significantly worse on both V-V and N-V conditions but performed similar to controls on N-N and V-N conditions, implying a verb generation deficit.

Present Study

The main purpose of the present study was to assess episodic memory and the strength and accuracy of feeling of knowing (FOK) judgments for nouns and verbs in PD patients versus healthy control participants. In addition, this study addressed the possible role of executive functions in FOK judgments.

Very few studies have examined noun and verb processing in PD and no study has evaluated whether memory or metamemory for verbs and nouns as to-be-learned material would be different. In this study, paired associate learning of two semantic classes of verbs (manipulable and non-manipulable) and of nouns (fruits and tools) as target words and neutral nouns as cue words were utilized and subjects were asked to make a FOK judgment for each item.

Souchay and colleagues (2006) found that accuracy of episodic FOK judgments was lower in PD patients than healthy controls. They assumed that this difference in accuracy was due to executive deficits in this population. However, they did not provide any empirical data to support this hypothesis. The first and the main novel aspect of this study was that two executive tests were correlated with metamemory accuracy: Wisconsin Card Sorting Test (Nelson, 1976) and verbal fluency tests which measure mental scanning and mental flexibility (e.g. Weintraub, 2000). Also, to further compare noun versus verb processing, action verbal fluency was measured and compared with semantic and lexical fluency.

Although several studies have examined cognitive processes in PD patients, many shortcomings arise from patient selection criteria. Parkinsonism may accompany several other neurological disorders which are not necessarily associated with the same cognitive impairment seen in PD. Moreover, PD patients may be prescribed drugs like anticholinergics which are known to interfere with cognitive functioning. (e.g. Dubois et al., 1987). The prevalence of depression is not low among PD patients and if not controlled for, questions about how much the impairment evidenced in a study is the consequence of Parkinson’s pathology may arise. Another important point is to use strict patient recruitment criteria to carefully discriminate between cognitive impairment associated with PD and PD dementia.

Hypotheses

The hypotheses of the present study are as follows:

1. The recall and recognition performances of PD patients will be low but recall and recognition of verb pairs will be lower than noun pairs only for PD patients.
2. The accuracy of FOK judgments will be lower for PD patients than healthy controls but FOK accuracy for verb pairs will be lower than noun pairs only in the PD group.
3. FOK accuracy will significantly correlate with executive measures in both PD and control groups.
4. PD patients will perform poorly on all fluency tests but the magnitude of difference will be greater between PD and control groups for the action fluency test.

CHAPTER 2: METHOD

Participants

Eighteen patients (3 female, 15 male) with a diagnosis of idiopathic Parkinson's disease, recruited from the outpatient clinic of İ.Ü. Istanbul Faculty of Medicine, Behavioral Neurology and Movement Disorders Unit and eighteen healthy age and education matched controls (6 female, 12 male) participated in this study. Exclusion criteria included the presence of another neurological condition, a history of substance or drug abuse, a Mini Mental State Examination (MMSE, Folstein, 1975) score of less than or equal to 23, and the presence of depression. Patients on only regular levadopa or dopaminergic agonist treatment and who responded well to this treatment were recruited; other medications like anticholinergics, MAO inhibitors, neuroleptics, non tricyclic antidepressants or any other drug known to interfere with cognitive functioning were not allowed for. Patients coming to the outpatient clinic were first evaluated by a staff neurologist to confirm the diagnosis of PD and those who reported subjective cognitive complaints were referred for neuropsychological screening. Cognitive screening consisted of 4 brief tests: Digit span forward and backward (Wechsler, 1997) to measure attention, Judgment of Line Orientation (Benton et al,, 1978) for visuospatial abilities, Logical Memory test (Wechsler Memory Scale-R; Wechsler, 1987) for memory, and Controlled Oral Word Association Test (Spreen & Benton, 1969, 1977) for executive functions. Patients who scored 1.5 SDs lower than age and education norms in at least 2 of these 4 tests and who were willing to participate were recruited for the present study. Therefore each participant in the PD group fulfilled the UK Parkinson's Disease Brain Bank criteria for idiopathic PD (Gibb & Lees, 1988); had subjective cognitive complaints and was documented to have objective cognitive impairment which was significant but not enough to qualify for a dementia diagnosis. Prior to testing, a neurologist with specialty in movement disorders assessed the severity of PD symptoms to confirm that only patients with Hoean &Yahr stages of I-III (mean= 1.33 SD= 0.48), which correspond to mild-moderate PD (Hoean& Yahr, 1968) were recruited. Mean UPDRS scores (only the motor subscale was administered) were 20.44 (SD= 9.15).

Eighteen neurologically healthy subjects (6 female, 12 male) volunteered in this study as controls. Control subjects were matched in terms of age and education with the patients; none of the control subjects were depressed or reported subjective cognitive complaints or were below the MMSE cut off score of 24. Table 1 shows the demographic characteristics of the participants. Although the mean Geriatric Depression Scale (GDS) scores of the PD group was significantly higher than the controls, none of the patients reached the clinical depression cut off score of 15 on GDS.

Materials

The stimulus booklet for the episodic memory and metamemory test consisted of 32 cue-target word pairs. The cue words were nouns whereas target stimuli were either verbs or nouns. Verb targets differed along the dimension of manipulability, half were manipulable verbs (defined as actions requiring fine hand movements or grasping) and the other half were non manipulable verbs. Half of the noun targets were from the category of fruits and the other from tools. Both target and cue words were matched between the four stimulus groups in terms of frequency of usage in the Turkish language (Göz, 2003). The final stimulus list was selected from a larger pool of word pairs which were pretested for degree of association. Word pairs rated as having a higher degree of association were eliminated and the final stimulus list consisted of 8 neutral noun-manipulable verb pairs; 8 neutral noun-non manipulable verb pairs, 8 neutral noun-tool pairs; and 8 neutral noun-fruit pairs. The cue words were written in lowercase letters and targets were written in capitals and were shown on an A4 size booklet. Word pairs from each of the four categories were randomly presented, and the order of presentation was the same for all participants

Procedure

Each participant was tested individually in a quiet exam room at the neuropsychology laboratory of İstanbul University, Istanbul Faculty of Medicine, Behavioral Neurology and Movement Disorders Unit. For all of the patients, the L-dopa or dopamine agonist therapy dosage had been stable for at least 4 weeks prior to testing. All patients were tested during their “on state”.

Subjects were shown 32 cue-target word pairs and were told that memory for these pairs would be assessed in an upcoming test. Each word pair was shown for 3 seconds and subjects were allowed two study trials. Immediately after the learning phase, subjects were shown the cue word and were asked to recall the target word. For each item subjects also made feeling-of-knowing judgments (a Yes/No judgment defined as the future likelihood of recognizing the target among distractors). After this phase, a recognition test was given. Each target item was presented with 3 foils: one semantically related, one phonemically related and one from a different pair in the same stimulus category. There was no time limit for the recognition test and participants completed it at their own pace. However, they were instructed to answer all of the questions. Following the paired associate learning paradigm the three verbal fluency tests were administered:

Semantic Fluency

Participants were asked to generate as many examples of animals in one minute as they could.

Lexical Fluency

The Controlled Oral Word Association Test (Spreen & Benton, 1969, 1977) was standardly administered with only one difference. Participants were given the letters K-A-S instead of F-A-S since there are more words starting with the letter K in the Turkish language and COWAT in the Turkish language is traditionally administered this way. For each letter the participants had one minute to generate as many words starting with that letter as they could but were instructed not to use proper names or derivatives (e.g. kalem, kalemlik, kalemsiz).

Action Fluency

Participants were asked to generate verbs in infinitive form and were given the following instruction adopted and revised from Piatt and colleagues (1999):

I'd like you to think about different actions . You have one minute again to tell me as many actions as you can. Can you give me an example of an action? (e.g. to laugh). Yes, that's the idea but I don't want you to use the same word with different endings, like laugh, laughing or laughs[1].

After participants completed the fluency tests, Wisconsin Card Sorting Task (WCST; Nelson, 1976) was administered. WCST was developed to assess executive functions such as shifting between and maintaining categories, problem solving and forming abstractions (Spreen & Strauss, 1991). The test consists of four stimulus cards and two decks of target cards (consisting of 64 cards each). Stimulus cards are placed in front of the subject and he/she is instructed to draw a target card from the deck and match it with one of the stimulus cards. The subject is only told whether his/her matching was correct or incorrect and s/he is supposed to sort the cards according to three dimensions (color, shape and number) which change in every consecutive 10 correct responses. Decreased performance in WCST may be due to not being able to take into account feedback provided by the examiner or perseverating on incorrect responses (McCarthy & Warrington, 1990). WCST performance is associated with frontal (executive) functioning (Lezak, 1995) and is sensitive to damage to the frontal lobes (Stuss et al., 2000). Several studies have shown that patients with PD are impaired in their WCST performance (Matsui et al, 2006; Owen et al, 1993; Rilling & Davis, 1999).

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[1]Bu testte sizden farklı eylemleri düşünmenizi istiyorum. Yine 1 dakikalık süreniz var ve bu süre içinde bana mümkün olduğunca fazla eylem saymanızı isteyeceğim. Bana bir eylem örneği verebilir misiniz? (örneğin gülmek). Evet aynen bu şekilde devam edeceğiz ama türetmenizi istemiyorum. Örneğin gülmek dedikten sonra güldüm, gülüyor gibi kelimeleri kullanamazsınız.

CHAPTER 3: RESULTS

To determine whether the dimension of manipulability of verbs yielded significant differences across the episodic memory and metamemory measures between patients with Parkinson's disease (PD) and normal control participants (NC) a series of 2 x 2 Repeated Measures Analysis of Variance (ANOVA) were calculated with group membership as the between subjects variable and target verb type as the within subjects variable. For recognition, there was a significant main effect of verb type due to non manipulable verbs being harder to recognize for both groups [F (1, 34) = 7.99, p=.008, η_p^2 =.19] but no significant interaction effect was observed. No such significant difference was observed for any other variable of interest. The same tests were run to compare tools and fruits as noun targets; no significant differences were observed. Hence data were collapsed to form two broader categories: verb and noun targets. In Tables 2 and 3 means and standard deviations for these categories are presented.

Episodic Memory

Recall

A 2x2 Repeated Measures ANOVA with group membership (PD vs. NC) as the between subjects variable and word type (verb or noun) as the within subjects variable was carried out to compare recall performance (proportion of correct recall). There was a significant group effect [F (1, 34) = 15.64, p<.001, η_p^2 =.32]. The PD group recalled fewer words than the NC group; the mean proportion of correct recall was .01 (SD = .01) for the PD group and .15 (SD = .15) for the NC group. There was not a significant effect of word type [*F* (1, 34) = .558, *p*=.46 η_p^2 =.02] or interaction [F (1, 34) = .02, p=.88 η_p^2=.001].

Recognition

The mean correct recognition proportion for the PD group was .45 (SD = .09) and it was .70 (SD = .14) for the NC group. With a 2x2 Repeated Measures ANOVA, recognition performance yielded a significant group effect [*F* (1, 34) = 45.53, *p*<.001 η_p^2 =.57] but no significant effect of word type [*F* (1, 34) = 2.74, *p*=.11 η_p^2 =.08] or interaction [*F* (1, 34) = 1.97, *p*=.17 η_p^2 =.06]. Figure 1 shows a bar graph of recall and recognition performances. Although word type or interaction effects were not significant, the bar graph shows that in the PD group there is a trend toward lower verb recall performance. Thus paired samples t-tests were run separately and revealed that, this difference was significant in the PD group [t (17) = -2.067, p=.054] but not significant for the NC group [t (17) = -.19, *p*=.853].

The PD group performed significantly better than the chance level, meaning that their recognition performances were significantly higher than .25 for verbs [t (17) = 5.27, *p*<.001] and nouns [t (17) = 8.63, *p*<.001].

In their study of metamemory in PD, Souchay et al. (2006) have also used a paired associate learning paradigm but applied a different recognition test in which they presented only the target words with an equal number of distractors. One could speculate that this does not measure recognition but familiarity. Nevertheless, to make recognition scores more comparable with their findings, a modified recognition score was calculated. In the recognition test of the present study, cue words were presented and the subject would have to choose the target word among 3 foils (one semantically related, one phonemically related and one from the same stimulus set). Thus each target word appeared twice in the test: one as the correct answer and one as the within stimulus set foil. In the familiarity score, if the subject chose the third type of foil, it was accepted as a correct response (since it reflects the subject's familiarity with the word). As can be seen in Table 4, PD groups familiarity scores for both verb and noun targets were comparable with those of the NC group with no significant group effect [F (1, 34) = 2.83, p=.10 η_p^2 =.08] or target type effect [F (1, 34) = 1.19, p=.28 η_p^2 =.03]. The finding that the familiarity score did not differ between the two groups implies that the PD group was more likely to misrecognize within stimulus set foils as correct. In fact a paired samples t-test revealed that the PD group significantly made more mistakes on such foils as compared to the control group [t (34) = 4.96, p<.001].

Metamemory

The Strength of Feeling-of-Knowing

Because FOK judgments were on a binary scale (Yes vs. No) following on earlier work with PD participants (e.g. Souchay, 2006), in this study the strength of FOK refers to the proportion of items that received positive or negative FOK judgments. Hence, FOK strength was calculated by dividing the total number of "Yes" predictions (items participants were not able to recall but felt that they would be able to correctly recognize in a subsequent test) by the total number of items.

Table 5 shows means and standard deviations for FOK strength. A 2 x 2 Repeated measures ANOVA revealed that group differences were significant (PD group was less likely to make Yes judgments) [F (1, 34) = 4.01, p=.053, η_p^2=.11] but there was no main effect of word type [F (1, 34) = 1.68, p=.20, η_p^2=.047] or interaction [F (1, 34) = .01, p=.932 η_p^2<.001].

Accuracy of Feeling-of-Knowing

The accuracy of FOK judgments were assessed by calculating the Goodman and Kruskal Gamma correlation between Yes/No FOK judgment and recognition of each item which yields a score between -1 and +1 for each subject (Nelson, 1984). Higher Gamma correlations correspond to high associations between FOK judgments and recognition performance for each item and hence higher metamemory accuracy; and zero corresponds to no association between predictions and recognition.

A 2 x 2 Repeated Measures ANOVA for FOK accuracy yielded no significant target type main effect [F (1, 32) = 1.4, p=.26, Partial η^2= .04] but a significant group effect [F (1, 32) = 10.01, p=.003, Partial η^2= .24] and interaction approached significance [F (1, 32) = 3.75, p=.06, Partial η^2= .11]. PD patients were significantly less accurate in their FOK judgments than the control subjects and they also tended to be less accurate for nouns (Fig.2). However, when a paired samples t-test was run separately for the PD group, this trend toward decreased accuracy for nouns did not reach the .05 significance level [t (16) = 1.93, p=.07].

Mean Gamma correlations for verbs and nouns were not significantly different from zero for the PD group, implying that their predictions were not above the chance level. However, Gamma was significantly higher than zero for controls (see Table 6)

The Goodman-Kruskal Gamma correlation is not the only measure used for comparing FOK judgments and recognition performance. Schraw (1995) has proposed that Gamma is a measure of association whereas the Hamman coefficient is a measure of agreement accuracy. He further suggested that both measures should be reported, especially in a study involving n x n data arrays (e.g. Yes/No FOK judgments). Thus Hamman coefficients (which also range from -1 to 1) were also calculated and analyzed.

A 2 x 2 Repeated Measures ANOVA for FOK accuracy as measured by the Hamman coefficient yielded similar results: There was not a significant target type main effect [F (1, 34) = .012, p=.91, η_p^2 <.001] but a significant group effect [F (1, 34) = 32.49, p<.001, η_p^2=.49] and a significant interaction [F (1, 32) = 6.38, p=.02, η_p^2= .16]. With Hamman coefficients, PD patients were significantly less accurate in their FOK judgments than the control subjects and they also tended to be less accurate for nouns (Figure 3). Also, PD group's Hamman coefficients were not significantly different from zero, whereas the NC group performed well above the chance level (Table 7).

Tables 8 and 9 provide proportional comparisons of FOK judgments and recognition performance for the whole task. PD patients as compared to the NC group were more likely to misrecognize items for which they gave a positive FOK and thus, were overconfident in their metamemory judgments. In other words, for items that the PD group gave positive FOK, percentage distribution of hits and misses were almost equal. On the other hand the control group had a higher ratio of hits for items predicted to be recognized. Recognition patterns for items with a negative FOK did not differ between PD and control groups.

The same comparisons were made for noun and verb targets separately (Tables 10-

13). The PD group tended to be more accurate about verbs for which they gave a negative FOK. The PD group's false alarm rates (correct recognition of negative FOK items) for verbs were less than those for nouns.

Executive Functions

Feeling of knowing judgments are shown to be related with functioning of the frontal lobes (executive functioning) (Pannu and Kazsniak, 2005). Thus, measures of executive functions were compared across PD and NC groups, and were correlated with FOK measures.

Fluency Tests

A question of interest in this study was whether and to what degree fluency tests are sensitive to cognitive changes associated with PD. To determine whether patients and controls performed differently in each of the fluency tests a 3x2 Repeated Measures ANOVA was computed with fluency tests (semantic, lexical and action) serving as the within subjects variable and group (PD versus control) serving as the between subjects variable. There was a significant main effect of fluency type [F (1, 68) = 82.38, p<.001, η_p^2=.71], a significant group effect [F (1, 34) = 12.81, p=.001, η_p^2=.27], and interaction approached significance [F (2, 68) = 3.029, p=.055, η_p^2=.08]. When independent t-tests were conducted, semantic fluency marginally differed between patients and controls [t (34) = -1.922, p= .063] whereas differences were significant for lexical fluency [t (34) = -3.679, p=.001] and action fluency [t (34) = -4.146, p<.001]. For the whole sample these three fluency tests were compared with paired sample t-tests: Action fluency was more difficult than semantic fluency [t (35) = 7.339, *p*<.001] and lexical fluency was more difficult than action fluency [t (35) = -4.60, *p*<.001]. Although the same pattern of test difficulty was observed in both groups, the difference between PD and control groups was most evident for the action fluency test (Table 14).

<u>Wisconsin Card Sorting Test</u>

As outlined in Table 15, PD patients completed significantly less categories, the percentage of perseverative errors was higher in the PD group, it took significantly more trials for them to complete the first category and the percentage of perseverative responses was lower for the PD group when compared to the control group.

<u>Executive Functioning and FOK Accuracy</u>

Pearson correlations between FOK accuracy and frontal functioning were conducted individually for the PD and control groups and are presented in Tables 16 and 17. These correlations were significant after controlling for age and education.

To further examine the relationship between executive measures and FOK accuracy, two composite z scores were calculated and regression analyses were carried out. Each of the verbal fluency measures (lexical, semantic and action) were converted to *z*-scores and averaged to form a composite fluency score. Similarly, a composite WCST *z*-score was calculated for the categories completed, percentage of perseverative errors and percentage of conceptual level responses. All of the composite scores were adjusted so that higher scores corresponded to better performance. As can be seen in Table 18, for the PD group, neither the fluency *z* score nor the WCST z score significantly correlated with gamma or Hamman measures. However, in the NC group WCST *z* score correlated with Hamman score (r= .6, *p*=.008) and gamma score (r= .462, *p*=.06) (Table 19).

In order to investigate how each composite executive score contributed to FOK accuracy, stepwise multiple regression analyses were performed separately for the PD and NC groups. Results for the PD group were not indicative of a significant regression equation for the gamma or Hamman coefficients as the dependent variable and composite executive scores as predictive variables. For the NC group, a stepwise multiple regression analysis with two composite executive scores (fluency and WCST) as the predictive variables and the Hamman coefficient as the criterion variable was computed. The regression yielded a significant equation that accounted for 32% of the variation in metamemory accuracy [adjusted R^2= 0.32, F (1, 17) = 9.02, p= .008] and only the WCST composite score entered the equation [β= .6, t (15) = 3.003, p= .008].

CHAPTER 4: DISCUSSION

The main question of interest in this study was to explore metamemory functioning for episodic memory in patients with cognitive impairment associated with Parkinson's disease (PD). Two related issues were also investigated: 1) Whether memory and metamemory for verbs and nouns would be differentially affected, and 2) whether and to what extend metamemory accuracy would be related with frontal functioning.

First of all, PD patients were significantly impaired in their recall and recognition of word pairs regardless of the target word type (i.e. verb versus noun). Several studies on verbal memory in PD have shown a deficit in free recall with relatively preserved recognition memory (Lezak, 1995; Pillon, 1993; Taylor &Saint-Cyr, 1995). Higginson and colleagues (2003) showed that recall impairment in the California Verbal Learning Test was associated with working memory deficits in PD patients. Bondi and colleagues (1993) compared performance of non demented PD patients and healthy controls on several tests of memory, executive functioning and perceptual abilities. They concluded that executive dysfunction predominantly accounted for the impaired performance on tasks measuring other cognitive domains. Specifically, memory impairment was significant only in more complex tests that required allocation of attentional resources, efficient learning strategies and planning. Given the effortful nature of the paired associate learning paradigm employed in this design, impaired performance in the PD group may be attributed to deficits in sustained attention and concentration.

In the recognition test of this study the target was presented with three types of foils.

(One foil was semantically related, one phonemically related and one was from the same stimulus set). Each target appeared twice in the test and if a PD patient acquired familiarity with a target, he was likely to choose the same word when it also appeared as the foil. Thus, PD patients were more likely than controls to choose the third type of foil. One could speculate that such a tendency reflects an inhibition deficit.

In terms of metamemory, subjects had to make a Yes/No judgment about their future likelihood of recognizing each target among distractors. FOK strength (i.e. proportion of Yes judgments) was significantly lower in the PD group which is in line with Souchay and colleagues' (2006) findings. When recognition patterns were carefully examined, it revealed a tendency of overconfidence in the PD group. PD patients had more misses and less hits for yes predictions when compared to controls. Furthermore, the accuracy of PD patients' judgments was significantly lower. This lack of metamemory accuracy in episodic memory was also in line with Souchay and colleagues' (2006) findings. In a review of metamemory studies on different neurological populations Pannu and Kazsniak (2005) have concluded that metamemory monitoring is most impaired in patients who have a disorder that involves a combination of frontal lobe dysfunction and memory loss (e.g. dementia), or in patients who have frontal lobe dysfunction and who have to engage in effortful episodic memory tasks. Thus, this present study also confirms that in an effortful episodic memory test (paired associate learning), PD patients are significantly impaired in metamemory monitoring.

PD patients' and control participants' memory and metamemory performances for verb and noun targets were also compared. Several authors have suggested that nouns and verbs are represented and processed in different neural networks (Damasio &Tranel, 1993; Shapiro et al., 2006; Tranel et al, 2005). Several case studies have shown verb processing deficits in patients with movement disorders (e.g. Bak et al., 2006; Silveri & Ciccarelli, 2007), speculating that motor systems and processing of action related words are interconnected. Cotelli and colleagues (2007) have shown that PD patients performed similarly with age matched controls on an object naming task but worse on action naming. The present design is exploratory in the sense that no study up to date has compared verbs and nouns as to-be-learned material.

There were no significant word type differences for recall. However, one should take into account the finding that recall performances of the PD group revealed a floor effect with the highest total recall being 3 out of 32. Presumably, performance impairment to such extent did not allow for noun verb comparisons. PD patients were able to recognize fewer verbs than nouns whereas no such difference was observed in the control group. This reveals episodic memory impairment for verbs in the PD group and is supportive of a lexical dissociation. Verb targets in this design were more poorly encoded only in the PD group. Thus, the difference may not be attributed to task difficulty effects as recognition proportions of verbs and nouns were very similar in the control group. PD patients are impaired in learning a new verb (Grossman et al., 1994), verb generation in response to a cue (Péran et al, 2003), and verb naming (Cotelli et al., 2007). This finding is further supportive of the selective verb processing deficit hypothesis in PD. Whether this recognition impairment is associated with a grammatical deficit (verbs as a lexical category are harder to process) or with an impairment in forming mental representations of actions is yet to be determined by future studies.

FOK strength for verbs and nouns was not different in either of the groups. When FOK judgments were compared with recognition performance, PD patients were slightly less accurate for noun targets. However, FOK accuracy measures for neither verbs nor nouns were not above the chance in the PD group. Since the PD group responded randomly for both lexical categories, it is not possible to attribute this difference to a dissociation between noun and verb processing. For items that PD patients gave a positive FOK, recognition proportions did not differ between verbs and nouns: of the items predicted to be recognized, PD patients were able to recognize half and failed to recognize the other half. However, PD patients were more likely to correctly recognize the nouns which they judged as they would not be able to recognize. PD patients had more false alarms and less correct rejections for nouns as compared to verbs. Although the proportion of "Yes" predictions did not differ for verbs and nouns, this pattern reflects a slight underconfidence for noun targets in the PD group. Since these results do not reach the .05 significance level, at this point it is not possible to determine whether they imply a selective metacognitive impairment for nouns or are a random correlational finding due to the small sample size.

When verbal fluency performances were compared, PD patients were able to generate less items in all three tasks (semantic, lexical and action fluency). However, the magnitude of this difference was greater for the action fluency task. Although lexical fluency was the hardest among these tasks, the action fluency test was better able to discriminate patients from controls. Piatt and colleagues (1999) have shown that the same pattern discriminated the PD dementia group from non-demented PD patients and controls. However, in their study cognitive impairment below the age norm in at least two of four cognitive domains (language, memory, executive function, visuoperceptual function) was defined as Parkinson's Disease Dementia. Not all PD patients with cognitive impairment fulfill the criteria for the diagnosis of dementia. In the present design, cognitive impairment associated with Parkinson's disease was discriminated from PD dementia on the basis of severity and whether the impairment interfered with activities of daily living. Nevertheless, the findings of both studies suggest that the action fluency test is more sensitive to the cognitive changes associated with Parkinson's disease and action fluency should become part of the neuropsychological assessment of PD patients.

PD patients were also impaired in various measures of the Wisconsin Card Sorting Task (WCST). The PD group completed significantly less categories, it took more trials for them to complete the first category, the percentage of perseverative errors were significantly higher and conceptual level responses were lower which correspond to an impairment in problem solving, set shifting, mental flexibility and abstract thinking.

Previous studies speculate that impairment in metacognitive monitoring is the result of frontal dysfunction (Pannu & Kazsniak, 2005) and that disruption of the fronto-striatal network should be responsible for the substantial decrease in episodic FOK accuracy in PD patients (Souchay et al., 2006). However, findings from this study do not reveal such a robust association. Among all the executive measures used in this study, in the PD group gamma only moderately correlated with lexical fluency and no significant regression could be equated. However, in the control group, WCST, which measures complex level executive functions, significantly correlated with gamma and explained 32% of the variability in Hamman coefficients. These findings in the control group show that metamemory accuracy is associated with executive functioning. The fact that executive impairment is not statistically associated with metamemory impairment in the PD group needs to be considered in detail. Speculatively speaking, complex level executive functions in PD patients is compromised to the extent that it is no longer predictive of another complex level functioning, metamemory monitoring.

CHAPTER 5: CONCLUSION

This study explored whether memory and metamemory for verbs would be differentially affected in patients with cognitive impairment associated with PD and whether impaired metamemory monitoring would be associated with executive deficits. Results show that PD patients perform significantly worse than healthy controls on recall and recognition in an effortful episodic memory task of paired associate learning. PD patients' overall metamemory monitoring is significantly impaired and they perform at the chance level in predicting recognition performance. The recognition performance of PD patients was significantly poorer for verbs, which supports the existing empirical evidence on impaired verb processing associated with Parkinson's disease. PD patients were also impaired in verbal fluency tests and the magnitude of difference from healthy controls was highest for the action fluency task. Generating action words is the most sensitive fluency measure for detecting PD related cognitive impairment and should be considered as a standard neuropsychological measure in evaluating this patient population. The PD group also performed poorly on the Wisconsin Card Sorting Test which measures complex level executive abilities like problem solving, abstract thinking and mental set shifting. Metamemory accuracy was associated with WCST performance in the control group whereas such a significant association between executive measures and accuracy was not found for the PD group.

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APPENDICES

APPENDIX A: TABLES

Table 1. Characteristics of Participants

	PD Patients n= 18	Controls n=18	t	p
Age	65.3 (10.08)	63.72 (9.39)	.49	.623
Education (years)	10.22 (4.61)	10.39 (4.30)	-.11	.911
MMSE	26.72 (2.40)	29.61 (.78)	-4.87	.001
GDS	5.55 (3.31)	.94 (1.43)	5.42	.001
Hoehn& Yahr stage	1.33 (.485)	-	-	-
UPDRS	20.44 (9.15)	-	-	-

Table 2. Means and Standard Deviations (in Parentheses) for Episodic Memory and Metamemory Measures of Manipulable and Non-Manipulable Verb Target Categories

	Group	
	PD	NC
recall for manipulable verbs	.03 (.07)	.32 (.31)
recall for non manipulable verbs	.007 (.03)	.28 (.29)
recognition for manipulable verbs	.43 (.18)	.77 (.16)
recognition for non manipulable verbs	.34 (.14)	.65 (.24)
FOK strength for manipulable verbs	.74 (.20)	.74(.20)
FOK strength for non manipulable verbs	.53 (.29)	.69 (.21)
Gamma for manipulable verbs	.20 (.91)	.72 (.33)
Gamma for non manipulable verbs	.17 (.90)	.52 (.55)

Table 3. Means and Standard deviations for Episodic Memory and Metamemory Measures of Tool and Fruit Noun Target Categories

	Group	
	PD	NC
recall for tools	.01 (.04)	.28 (.30)
recall for fruits	.01 (.04)	.29 (.29)
recognition for tools	.49 (.17)	.72 (.21)
recognition for fruits	.49 (.17)	.72 (.21)
FOK strength for tools	.56 (.32)	.68 (.26)
FOK strength for fruits	.50 (.27)	.69 (.22)
Gamma for tools	.004 (.75)	.83 (.35)
Gamma for fruits	.05 (.84)	.48 (.76)

Table 4. Familiarity Scores for Verbs and Nouns.

	Group	
	PD	NC
Familiarity for verbs	12.06 (2.7)	13.53 (1.42)
Familiarity for nouns	13.00 (2.61)	13.29 (1.99)

Table 5. FOK Strength for Verbs and Nouns

	Group	
	PD	NC
FOK strength for verbs	.56 (.28)	.72 (.19)
FOK strength for nouns	.53 (.27)	.68 (.22)

Table 6. Means, Standard Deviations and t-test Values (Compared with Zero) for Mean Gamma Accuracies

	Target type	Mean gamma (SD)	t	p
PD	Verb	.348 (.73)	1.98	.07
	Noun	-.041 (.63)	-.28	.79
NC	Verb	.57 (.33)	7.19	<.001
	Noun	.66 (.47)	5.77	<.001

Table 7. Means, Standard Ceviations and t-test Values (Compared with Zero) for Mean Hamman Coefficients

	Target type	Mean gamma (SD)	t	p
PD	Verb	.069 (.33)	0.89	.38
	Noun	-.049 (.24)	-.88	.39
NC	Verb	.43 (.32)	5.58	<.001
	Noun	.53 (.22)	10.22	<.001

Table 8. Comparison of FOK Judgments and Recognition for PD Patients

FOK \ RECOGNITION	YES	NO
YES	.47	.53
NO	.43	.57

Table 9. Comparison of FOK Judgments and Recognition for Controls

FOK \ RECOGNITION	YES	NO
YES	.79	.21
NO	.42	.58

Table 10. Comparison of PD Group's FOK Judgments and Recognition for Verbs

FOK \ RECOGNITION	YES	NO
YES	.46	.54
NO	.32	.68

Table 11. Comparison of NC Group's FOK Judgments and Recognition for Verbs

FOK \ RECOGNITION	YES	NO
YES	.77	.23
NO	.41	.59

Table 12. Comparison of PD Group's FOK Judgments and Recognition for Nouns

FOK \ RECOGNITION	YES	NO
YES	.46	.54
NO	.47	.53

Table 13. Comparison of NC Group's FOK Judgments and Recognition for Nouns

FOK \ RECOGNITION	YES	NO
YES	.85	.15
NO	.43	.57

Table 14. Means and Standard Deviations for Verbal Fluency Tests

Fluency type	Group		Comparisons	
	PD	NC	t	p
semantic fluency	18.5 (6.82)	22.56 (5.8)	-1.92	.06
lexical fluency *	8.04 (3.59)	13.62 (5.35)	-3.68	.001
action fluency	10 (5.66)	17.83 (5.68)	-4.15	<.001

* Total number of words starting with letters K, A and S divided by three

Table 15. Means, Standard Deviations and Independent Samples t-test Comparisons across PD and NC Groups for WCST Measures

WCST measures	Group		Comparisons	
	PD	NC	t	p
categories	1.11 (1.29)	3.83 (1.95)	-4.96	<.001
percentage of perseverative errors	34.40 (15.10)	20.43 (11.21)	3.15	.003
trials to complete first category	62.50 (54.58)	30.94 (32.94)	2.10	.04
percentage of conceptual level responses	23.31 (12.90)	52.69 (24.60)	-4.49	<.001

Table 16. Correlations between Gamma and Executive Measures for the PD Group

	Semantic fluency	lexical fluency	action fluency	categories WCST	% perseverations WCST	trials to complete first category in WCST	% conceptual level responses WCST
gamma accuracy	.297	.489 *	.435	-.214	-.025	.259	-.118
Semantic fluency		.730 **	.625 **	-.054	-.305	-.089	.289
lexical fluency			.669 **	-.164	-.204	.230	.103
action fluency				-.130	-.305	.288	.108
categories WCST					-.282	-.706 **	.713 **
% perseverations WCST						.365	-.565 *
trials to complete first category WCST							-.646 **

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Table 17. Correlations between Gamma and Executive Measures for the Control Group

	Semantic fluency	lexical fluency	action fluency	categories WCST	% perseverations WCST	trials to complete first category in WCST	% conceptual level responses WCST
gamma accuracy	-.117	.099	.011	.665 **	-.521 *	-.483 *	.617 **
Semantic fluency		.652 **	.661 **	.082	-.186	.040	.194
lexical fluency			.788 **	.294	-.345	.031	.417
action fluency				.104	-.155	.150	.239
categories WCST					-.796 **	-.733 **	.937 **
% perseverations WCST						.688 **	-.885 **
trials to complete first category WCST							-.693 **

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Table 18. Correlations between Gamma, Hamman and Executive Composite Scores for the PD Group

		zWCST	zFluency
Gamma	r	-.12	.31
	p	.65	.23
Hamman	r	-.27	.37
	p	.27	.12

Table 19. Correlations between Gamma, Hamman and Executive Composite Scores for the NC Group

		zWCST	zFluency
Gamma	r	.46	.13
	p	.06	.61
Hamman	r	.60	.47
	p	.008	.05

APPENDIX B: FIGURES

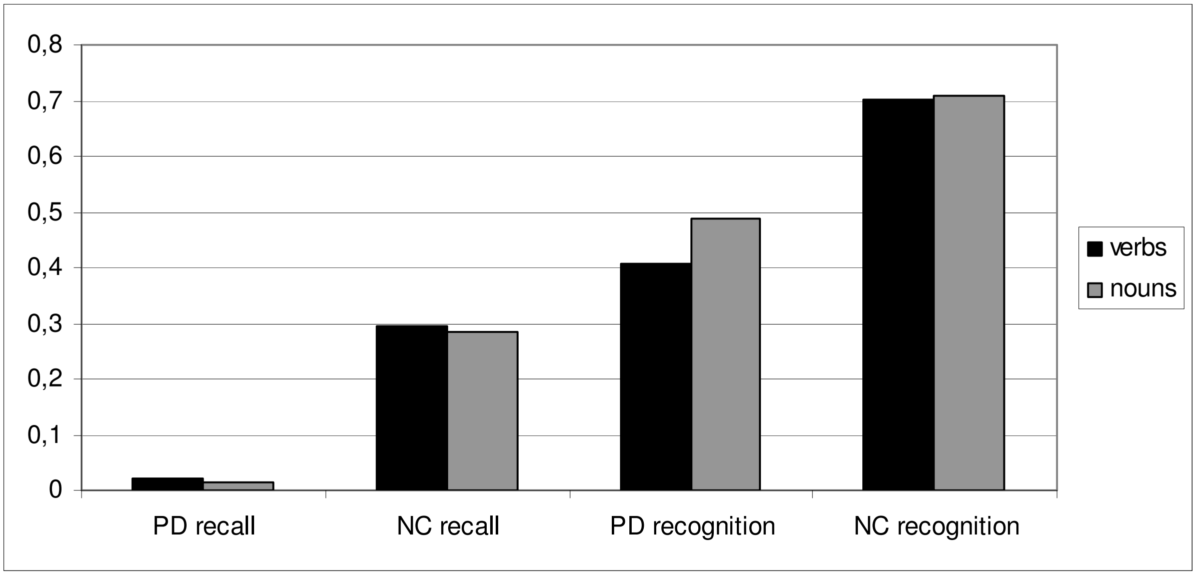

Figure 1. Mean recall and recognition ratios of verbs and nouns for PD and control groups.

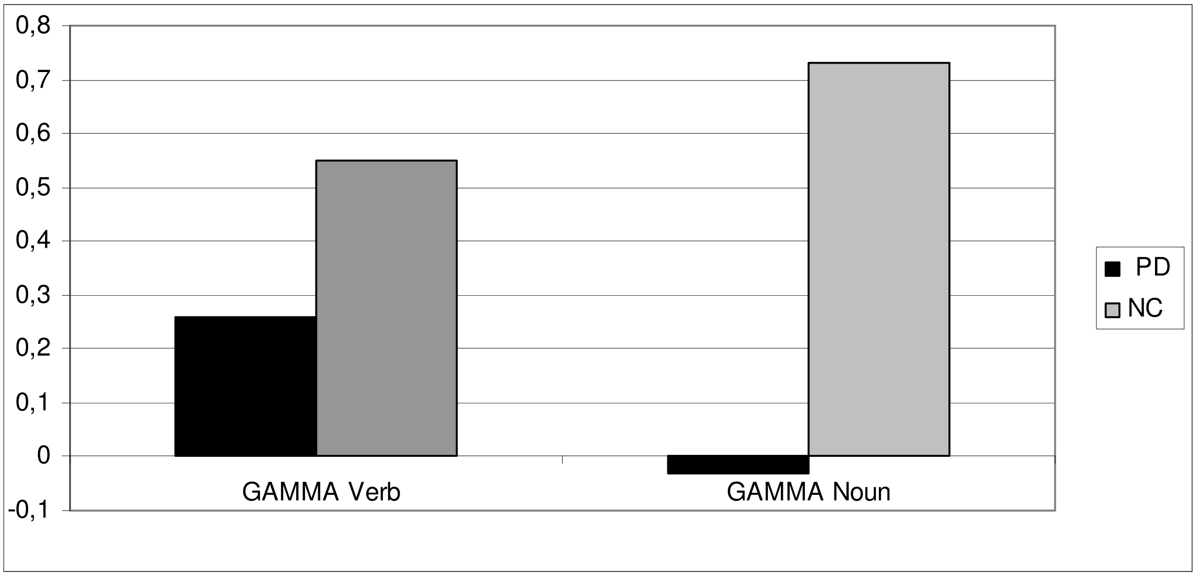

Figure 2. Mean Gamma Scores of Verbs and Nouns for PD and Control Groups

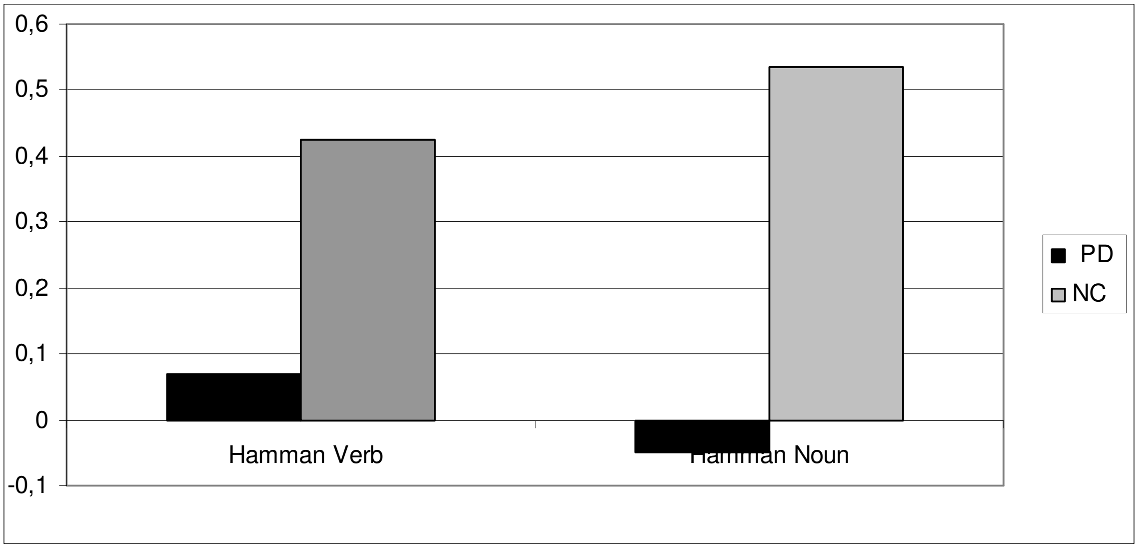

Figure 3. Mean Hamman coefficients of verbs and nouns for PD and control groups

APPENDIX C: STIMULUS LIST FOR THE PAIRED ASSOCIATE LEARNING PARADIGM

Kadeh – İLİKLEMEK
İklim – FIRÇALAMAK
Miras - DOKUMAK
Yüzük – KATLAMAK
Taksi - OVMAK
Havuz – ÜTÜLEMEK
Heykel – ÖRMEK
Ceket – ALKIŞLAMAK
İpek - DİRİLMEK
Köpük - YALVARMAK
Sergi - ÖKSÜRMEK
Nehir - ŞİŞİRMEK
Gömlek - HAVLAMAK
Yastık - DAMLAMAK
Bulut - ZIPLAMAK
Gündüz – KANAMAK
Gurur - KARPUZ
Barış – ARMUT
Pilot - ÇİLEK
Balkon - MANDALİNA
Hasar - KİRAZ
Fırça - BÖĞÜRTLEN
Dere - ANANAS
Kimya - İNCİR
Cisim - MATKAP
Bayrak -TORNAVİDA
Dosya - KÜREK
Zihin - BALTA
Yakıt - ÇAPA
Şapka- BALYOZ
Zarf - ÇEKİÇ
Deyim - CETVEL

APPENDIX D: RECOGNITION TEST

1. Ceket - (?)

a. Alkışlamak b. Nakkaşlık c. Kutlamak d. Ütülemek

2. Balkon – (?)

a. Portakal b. Mandalina c. Böğürtlen d. Mandal

3. Yüzük – (?)

a. Saklamak b. Katlamak c. Dokumak d. Kıvırmak

4. Bayrak –(?)

a. Tornavida b. Çivi c. Tornistan d. Kürek

5. Gömlek- (?)

a. Miyavlamak b. Damlamak c. Horlamak d. Havlamak

6. Hasar – (?)

a. Kiraz b. Biraz c. Vişne d. Ananas

7. Bulut – (?)

a. Hoplamak b. Zırnık c. Zıplamak d. Öksürmek

8. Havuz – (?)

a. Kötülemek b. Alkışlamak c. Ütülemek d. Düzeltmek

9. Yakıt – (?)

a. Çapa b. Çatı c. Dümen d. Balyoz

10. Fırça- (?)

a. Dut b. Böğürtlen c. Karpuz d. Söğüt

11. Köpük – (?)

a. Yalvarmak b. Ağlamak c. Yaver d. Şişirmek

12. Miras – (?)

a. Dikmek b. Sokulmak c. Fırçalamak d. Dokumak

13. Dere- (?)

a. Ananas b. Anne c. Armut d. Avokado

14. Taksi – (?)

a. Soymak b. Ovmak c. Alkışlamak d. Çitilemek

15. Deyim – (?)

a. Evvel b. Cetvel c. Gönye d. Matkap

16. Kimya – (?)

a. İncir b. Kiraz c. Zincir d. Üzüm

17. Cisim –(?)

a. Matbaa b. Delgeç c. Matkap d. Balta

18. Heykel - (?)

a. Örmek b. Görmek c. Kurcalamak d. Eğirmek

19. Dosya – (?)

a. Kürek b. Kazma c. Cetvel d. Yürek

20. Yastık – (?)

a. Daralmak b. Yalvarmak c. Yudumlamak d. Damlamak

21. Zihin - (?)

a. Balta b. Yafta c. Salata d. Çapa

22. Gündüz – (?)

a. Yaralanmak b. Panama c. Zıplamak d. Kanamak

23. Sergi – (?)

a. Dirilmek b. Tıksırmak c. Öksürmek d.Yüksünmek

24. Şapka- (?)

a. Tornavida b. Balayı c. Delgeç d. Balyoz

25. İklim - (?)

a. Dokumak b. Fırçalamak c. Taramak d.Saçmalamak

26. Barış – (?)

a. Armut b. Ahlat c. Elma d. İncir

27. Nehir – (?)

a. Şaşırmak b. Kanamak c. Üflemek d. Şişirmek

28. Zarf – (?)

a. Kürek b. Çakır c. Çekiç d. Testere

29. Kadeh – (?)

a. İliklemek b. İsilik c. Düğmelemek d. Örmek

30. Gurur – (?)

a. Kavun b. Karpuz c. Mandalina d. Topuz

31. İpek – (?)

a. Durulamak b. Dirilmek c. Havlamak d.Canlanmak

32. Pilot – (?)

a. Armut b. Dilek c. Çilek d. Frambuaz