Cortico-striatal circuitry in visual perception

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subjects. Subject had to decide whether a picture, presented for 30 ms, contained animal or not, by pressing one of the two response buttons. In normal control subjects there was a sharp difference between the responses evoked by animal and non-animal pictures, peaking around 200 ms (N1). Parkinson's disease (PD) patients showed no differential responses, non-animal responses were not more negative than animals. In the Huntington's disease (HD) group the responses differed for target and distractor stimuli as in the healthy subject at all electrode sites but the lateral temporal electrode sites. Between group comparison demonstrated that the N1 amplitudes were significantly smaller for both kind of stimuli in the HD group. In the Alzheimer's disease (AD) group the non-animal pictures evoked more negative responses as well as in the control group. These results are interesting from the point of view that the general mental status of the AD patients was far worse. The difference between the pictures was present in demented AD patients with severe clinical symptoms and cognitive decline, while it was absent in non-demented PD patients with much better general cognitive functioning. On the bases of these results we suggest that the striato-cortical pathways, which are between the primary affected structures in PD play a crucial role in the early categorization processes. Contrary the long cortico-cortical pathways of which disruption is the main feature of AD are not critical for this kind of ultra rapid visual categorization. Pathways damaged in HD seem to play minor role in the ultra-rapid categorization because the differential response is spared. Since several neuroanatomical studies directed attention toward the closed-loop interconnection of the temporal lobe and the striatum, the deficiency in the temporal electrode sites of the early electrical signs of the categorization process probably attributed to the basal ganglia pathology. On the other hand, the general amplitude diminution of the potentials evoked by both kinds of stimuli may be related to the widespread cortical degeneration that was described in HD.

In the second experiment we have examined the role of the fronto-striatal system in the implicit leaning. Recently, the probabilistic classification learning (PCL) task has been introduced as a promising tool to investigate implicit learning functions. In this task subjects learned which of two outcomes would occur on each trial after presentation of a particular combination of cues. The relationship is not absolute: cues and outcomes are

statistically related. During the task individuals learns gradually the statistical probability of the given combination, without having conscious knowledge about the rule.

In order to modulate the activity of the fronto-striatal system we have applied transcranial direct current stimulation (tDCS) over the prefrontal cortex for 10 minutes. tDCS known to be a useful noninvasive method to up- or down-regulate the underlying cortical excitability, depending on the current direction. The effectiveness of the tDCS has been proved over the motor as well as the visual cortex. Transcranial direct current stimulation (TMS) induced motor evoked potentials were decreased by cathodal stimulation and was increased by anodal stimulation. In the visual system Antal et al. has showed that cathodal stimulation of the occipital cortex can decrease the contrast sensitivity, and the amplitude of the primary visual evoked potential, and increase the threshold of the TMS evoked phosphenes. The plastic changes caused by tDCS have been related to N-methyl-D-aspartate (NMDA) receptors, while NMDA-receptor antagonist dextromethorphan suppressed the post-stimulation effects of both anodal and cathodal DC stimulation, in humans.

10 min anodal stimulation resulted in an improvement of the implicit learning of the task, while cathodal stimulation failed to reach any significant effect. We suggest that this improvement was due to the plastic changes in the fronto-striatal circuit evoked by the increased neuronal excitability.

The role of the basal ganglia formation in visual perception and cognition was investigated intensively over the last decades. Indeed, there are some evidences to suggest that the basal ganglia play role in both the complex visual object cognition and visuospatial cognition. Receiving inputs from the ventral and dorsal stream, sending and receiving information to and from the frontal areas, makes the basal ganglia complex an ideal structure to organize the incoming sensory information on the basis of behavioral requirements which probably stored in the frontal cortex working memory system. In this way the striato-cortical network is an indispensable connecting point of the categorization processes irrespectively of the explicit or implicit nature of the process.

Original papers related to the thesis

Antal A, Nitsche MA, Kruse W, **Kincses ZT**, Hoffmann KP, Paulus W (in press) Direct current stimulation over V5 enhances visuo-motor coordination by improving motion perception in humans. J Cogn Neurosci.

Antal A, Nitsche MA, **Kincses ZT**, Lampe C, Paulus W (in press) No correlation between moving phosphene and motor thresholds: a transcranial magnetic stimulation study. Neuroreport.

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Contents

List of abbreviations

(r)TMS	(repetitive) Transcranial magnetic stimulation
AD	Alzheimer's disease
ADL	Activity of daily living
ANOVA	Analysis of variance
CAG	Cytosine adenosine guanine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition
EEG	Electroencephalogram
EOG	Electro-oculogram
ERP	Event related potential
fMRI	Functional magnetic resonance imaging
GABA	Gamma butyric acid
HD	Huntington's disease
HDC	Huntington's disease mutation carriers
MAO-B	Mono-amine oxidase -B
MEG	Magnetoencephalogram
MMSE	Mini mental state examination
NMDA	N-methyl-D-aspartate
PCL	Probabilistic classification learning
PD	Parkinson's disease
PET	Positron emission tomography
PFC	Pre-frontal cortex
PIT	Poterior-inferior temporal cortex
RT	Reaction time
SPECT	Single photon emission computer tomography
tDCS	Transcranial direct current stimulation
UPDRS	Unified Parkinson's disease rating scale
V1	First visual cortex
V2	Second visual cortex

Introduction

Categorization

Categorization, meaningful organization of the surrounding environment plays crucial role in our everyday life. It reduces the amount of information we have to process, and allows us to draw inferences about imperceptible properties. Categorization may be what makes possible human perception, memory, communication, and thought as we know it. Review of the literature suggests at least three distinct procedures playing role in categorization (Smith et al., 1998). In the first case, category membership is decided on the basis of rules describing the category (the rules specifies the necessary and sufficient conditions for category membership) (Smith and Sloman, 1994). Another possibility is the similarity based categorization, when the subjects have to determine the overall similarity of the test object to a remembered exemplar of the category (Nosofsky, 1989; Nosofsky and Johansen, 2000). The third possibility is the prototype similarity, when the subject has to determine the level of similarity compared to a stored virtual prototype, an average central tendency of the category (Shepard, 1987).

Several studies emphasized the dissociation between the rule based and similarity based categorization (Smith et al., 1998; Maddox et al., 2003). A recent fMRI study suggested that when the categorization was based on well defined rules or overall similarity, different brain areas were activated (Grossman et al., 2001). The authors described a greater recruitment of the left dorsolateral prefrontal cortex and a unique recruitment of the right ventral frontal cortex and the thalamus in the rule based categorization. The similarity-based categorization was associated with right inferior parietal activation. Another study reported about dissociation of the rule-based and similarity based strategies in Parkinson's disease, pointing out the importance of the striato-cortical network in the rule based processing (Ashby et al., 2003). Patients were highly impaired compared to the age-matched control group, in the rule-based categorization task but were not different from the controls in the similarity-based task. Furthermore, a well known phenomenon is the difficulties of patients with frontal-lobe pathology and Parkinsonian patients to perform Wisconsin Card Sorting Test (Green et al., 2002). In this

test subjects have to learn the rules stated by the experimenter and switching between them whenever the experimenter changes the rules explicitly.

Another dissociation can be found between the prototype and exemplar based categorization. Kolodny (Kolodny, 1994) compared normal controls and medial-temporal-lobe and Korsakoff's amnestics on two different categorization tasks. One task involved paintings, which had to be categorized after a learning phase, on the base of the different painters. Prior research indicated that categorization in this task was based on exemplar-similarity; indeed paintings done by the same painter were sufficiently dissimilar that it is difficult to even generate a plausible prototype for each artist. In the next task subjects were presented to a set of dots generated by statistical distortion one of the prototype patterns. In the learning phase subjects were informed in which of the categories each pattern belonged. In a subsequent test-phase, the subjects were presented the learned patterns plus novel ones, than asked to indicate appropriate category for each one. This task is typically interpreted in terms of prototype similarity. Amnestic patients in the painting task were far worse than controls, but in the other task, in which dot patterns were presented, patients performed as well as healthy subjects. Similar results were presented by Squire and Knowlton in connection with amnestic patients (Knowlton and Squire, 1993) and a profoundly amnestic patient (E.P.) (Squire, 1994). In Alzheimer disease (AD) Keri et al. (Keri et al., 2002b) presented data about the impairment of the explicit recognition of the dot patterns. However the implicit categorization functions were also disrupted, this was selective for the prototype stimuli; the categorization of the non-prototype dot pattern stimuli was spared.

Presenting a holistic picture about the categorization process, many neuroimaging and electrophysiological studies provided evidence for a discrete categorical organization of the brain. In particular, there are specific representations of faces in the occipito-temporal cortex and the fusiform face area (Ojemann et al., 1992; Allison et al., 1994b; Allison et al., 1994a; Clark et al., 1996; Puce et al., 1996; Kanwisher et al., 1997; Schendan et al., 1998; Allison et al., 1999; Kanwisher, 2000; Goffaux et al., 2003), human body in the lateral occipito-temporal cortex (Downing et al., 2001), animals in the right fusiform cortex (Kawashima et al., 2001), buildings in the right lingual sulcus (Aguirre et al., 1998), man-made tools in the left posterior middle temporal cortex (Moore and Price,

1999), plants in the right lateral occipital cortex (Kawashima et al., 2001). Contradictory, some authors claim that semantic systems are undifferentiated by categories at neural level. For example, Devlin et al. in subsequent fMRI and PET studies failed to find robust evidence of functional segregation by domain or categories (Devlin et al., 2002).

Whether people use a variety of categorization procedures ('multiple-view') or is all human categorization based on a single procedure ('unitary-view') (Shepard, 1987) is still a matter of debate.

Ultra rapid visual categorization

Recent research has demonstrated an unexpectedly fast processing of visual information (Thorpe et al., 1996). For example, it is known that higher order visual areas such as the primate superior temporal sulcus contain neurons that can respond selectively to faces with latencies of ~100ms (Oram and Perrett, 1992). Freedmann et al. found neurons in the monkey prefrontal cortex (PFC) responding category selectively in about 100ms (Freedman et al., 2001). The monkeys were presented with 'doglike' and 'catlike' pictures generated by computer morphing the two basic forms along a continuous line. They reported that many PFC neurons responded selectively to the different types of visual stimuli belonging to either the cat or the dog category and with the same strength, regardless of how morphologically close the image were to the other category. These neurons most certainly receive their input from the inferior temporal cortex, which lies at or near the final stage of the ventral visual pathway. Even thought the lack of the category specificity (Vogels, 1999a, b), these neurons are known to respond highly selectively to particular visual stimuli, such as faces or even different views of the same object in about 100 ms (Sato et al., 1980; Sary et al., 1993; Vogels and Orban, 1996).

In humans a growing evidence indicates that ERP components in the 150-200ms range reflects the initial perceptual processing and categorization of stimulus patterns such as faces, word-forms (e.g. letter strings) and pictures of animals (Thorpe et al., 1996; Schendan et al., 1998). For example face selective responses can be evoked in 170ms (Goffaux et al., 2003). The source of this face specific activity is probably in the fusiform gyrus, proved by several fMRI (Haxby et al., 1991; Sergent et al., 1992; Haxby et al., 1994; Puce et al., 1995; Clark et al., 1996; Puce et al., 1996; Courtney et al., 1997;

Kanwisher et al., 1997), EEG and MEG source analysis studies (Watanabe et al., 1999) as well as in epilepsy patients with implanted subdural electrodes (Ojemann et al., 1992; Allison et al., 1994b; Allison et al., 1994a).

In the study of Thorpe and his co-workers pictures of natural scenes containing animal and non-animal images were presented for 20ms (Thorpe et al., 1996). Subjects performed a go/no-go categorization task in which they had to decide whether the image contained an animal or not. By comparing the average brain potentials generated on correct go trials with those generated on correct no-go trials the authors were able to demonstrate that the two potentials diverge very sharply at ~150 ms after the stimulus onset. The effect was particularly clear at frontal recording sites, and was characterized by a nearly linear increase in voltage difference over the following 50 ms or so, the potential being more negative on no-go trials. Later investigations proved that this was not due to an exclusive, 'hard–wired' processing of the evolutionary important animal category, because the same kind of potential difference could have been obtained with different supraordinal categories also (e.g.: animals vs. vehicles) (VanRullen and Thorpe, 2001). Concerning the reaction times obtained in the same task, the median reaction time was 445 ms ranging between 382-567 ms. In a later study of Van Rullen et al. (VanRullen and Thorpe, 2001) with a more detailed method (increased size of the images and with a touch sensitive plate instead of a computer mouse) the authors recorded reaction times for the target stimuli with the median value of slightly above 350 ms. Monkeys have proved even faster, with mean reaction time around 250 ms, and a bias towards correct responses starting before 200 ms (Fabre-Thorpe et al., 1998).

Antal et al. confirmed the result of Thorpe at al. using a similar task (Antal et al., 2000). In this later paradigm the subjects had to press different buttons for animal and non-animal items instead of the go/no-go version, ruling out the unbalanced motor demands. In this version of the task also as in the former studies of Thorpe et al. the early potential differences were found not only at frontal but at temporal and parietal electrode sites also stressing the magnitude of the effect. On the other hand, the difference became significant first at left frontal electrode. Repeating the experiment with simple luminance gratings in which subjects had to discriminate between two different spatial frequencies, the early

potential difference could be seen only at frontal electrode sites for a short period. This difference probably due to the decision making process.

Although the direct comparison of the two paradigms is not available yet, the fact that not only the no-go response related to distractor stimuli but also distractors related to separate but same type of motor response evoked more negative potentials, argues against the hypothesis of Thorpe et al. (Thorpe et al., 1996) who suggested that the early frontal differential response is due to the inhibition of the inappropriate behavioral response. Nevertheless, the category specific activity at frontal recording sites at 150 ms implies that a great deal of visual processing must have been completed before this time. Even if not whole process of object detection is needed for this kind of early categorization, but feature weighting is also enough, the visual system still has to process an enormous amount of information. Not only has the target detection to be completed at this stage, but enough information had to be collected to conclude that there is no animal on the picture. How the visual system is able to perform such a phenomenal amount of computation in such a short interval, is clearly a challenge for current theories of object vision. Taking into account the large number of stages across the visual processing, it seems that much of this processing must be based on essentially feed-forward mechanisms. Regarding to the reaction times and the differential activity in the ERP, the detection of object belonging to the target category can be done almost as fast as in a simple perceptual signal detection task. A very tempting interpretation of these results is that categorization does not occur after object perception but parallel with that. Partly the two processes, at the beginning of the information processing have to share common resources in the brain but later on the object recognition and the feature weighting based categorization may happen in different networks.

What's more these complex natural images can be processed and categorized in parallel without the need of sequential attention (Rousselet et al., 2002). Both electrophysiological and behavioral data show that subjects were as fast at responding to two simultaneously presented natural images as they were to a single one. Neither the median reaction times nor the latency of the differential activity in the ERP was longer when the two pictures were presented together. The authors argued that the slight

worsening in the accuracy was due to the common motor output which is the bottleneck after the separate parallel processing of each item.

It seems that familiarity or expertise has no effect on this kind of ultra rapid categorization. 3 weeks of extensive training failed to increase the speed of the categorization: Completely novel scenes could be categorized just as fast as highly familiar ones (Fabre-Thorpe et al., 2001). On the other hand, there was no difference in either the onset latency of the differential activity or its slope for familiar and for novel images, just the amplitude of the activity was slightly larger for familiar stimuli, but this effect was not evident until 30-50 ms after the start of the differential response. All these results suggest that this early categorization process is highly optimized. The fact that the chromatic information has no effect on this kind of categorization task (Delorme et al., 2000) implies that the luminance based information reaches the cortex through the magnocellular pathway -before the chromatic information through the parvocellular pathway- is enough for the early categorization processes.

These studies, mentioned above suggest that this extremely fast visual processing is hardly possible with those models in which neurons transmit information as a rate code. Within this short time the information must be passed through the retina, and LNG and several other cortical areas, including V1, V2, V4, PIT etc. and in each of which two synaptic stages at least must be involved. Furthermore, conduction velocities of intracortical fibers are known to be remarkably slow (e.g. < 1 m/s) (Nowak et al., 1997). These things above altogether leave less than 10 ms for computation in each processing stage which raises doubt about the rate coding model. Because of this incompatibility, Thorpe et al. recommended to take into account the order, pattern and precise timing of firing also (Thorpe et al., 2001; VanRullen and Thorpe, 2002). The base of their Rank Order Coding model is that strongly activated neurons tend to fire first. In this model neurons can be made sensitive to the order of activation of their inputs by including a feed-forward shunting inhibition mechanism that progressively desensitizes the neuronal population during a wave of afferent activity. In such case, maximum activation will only be produced when the afferent inputs are activated in the order of synaptic weights. With this highly efficient model complex visual processing tasks can be implemented in purely feed-forward fashion, neurons having time only to fire one spike.

What are the neural correlates of this categorization processes? A recent event related fMRI study (Fize et al., 2000) suggests that this early potential difference is an electrophysiological correlate of differential activation in the right occipito-parietal sulcus, posterior parahippocampic gyri on both sides, left fusiform gyrus and median occipital gyrus, elicited by animal and non-animal scenes. These results are in agreement with the source analysis result published by Fize et al. (Fize et al., 1998). They found that the differential activity is correlated with two dipole sources located in the occipitotemporal regions. The methodological difficulties of the two above mentioned studies (low temporal resolution of the fMRI technique and the infinite solution of the inverse problem) raise the question whether the observed differential activities and the sources are reliable neural correlates of the ultra-rapid categorization.

There are two critical issues that may play a central role in the rapid categorization of natural scenes. First, long cortico-cortical pathways may transfer information between primary and extrastriate visual cortices in ventral stream for higher-level image analysis. This mechanism thought to be essential for the processing of complex multidimensional stimuli to complete target identification (Thorpe et al., 1996; Antal et al., 2000; Fize et al., 2000). Second, cognitive models suggest that in some circumstances categorization is based on feature weighting, that is, attributes relevant to a given category are analyzed selectively or pronouncedly and then are linked to specific decision rules (Gati and Tversky, 1984; Murphy and Medin, 1985; Caramazza and Shelton, 1998; Schyns et al., 1998). In the case of animal non-animal categorization task, subjects may extract and integrate characteristic features of animals instead of detailed processing of all available perceptual details. Feature weighting and decision binding processes are hypothesized to be mediated by cortico-striatal circuits (Ashby et al., 1998; Kropotov and Etlinger, 1999). To elucidate the further characteristic of these feed-forward connections in the ultra rapid visual categorization we conducted the animal non-animal categorization paradigm in several neurodegenerative patient groups.

Alzheimer's disease

The first group included patients with Alzheimer's disease (AD). AD is the most common degenerative disease of the brain, incurring to an increasing degree an immerse

societal impact. The major symptom is the gradual development of forgetfulness resulting in severe intellectual deterioration. The failure of the retentive memory, the dysnomia, visuospatial disorientation and personality changes are among the most prominent signs of the disease. Neuropathologically, the primary and the earliest site of lesion can be detected in the mesial temporal lobe, resulting in a profound and progressive clinical amnesia (Huff et al., 1987; Braak and Braak, 1991; Welsh et al., 1992; Braak and Braak, 1995; Mori et al., 1997). In the advanced stages of the disease, the brain presents a diffusely atrophied appearance. Neocortical damage in AD involves predominantly association cortex which becomes progressively deafferented of cortical and subcortical inputs and devoid of some locally projecting intrinsic cortical neurons (Henderson and Finch, 1989). The degree of synaptic loss in the frontal, parietal and temporal association cortex has been found to correlate with the severity of the cognitive impairment (Terry et al., 1991) Electrophysiological studies described increased background electroencephalographic slowing with a reduction in fast activity (synchronization) and changes in the brain electrical activity over the parietal and temporal areas (Duffy et al., 1984). EEG coherence is found to be decreased between the parietal and frontal areas, presumably due to degeneration of the long cortico-cortical fibers that connect the parietal association and frontal areas (Leuchter et al., 1992). PET has indicated hypometabolism within the association cortex, with relative sparing of primary motor and sensory areas (Duara et al., 1986; Haxby et al., 1986; Horwitz et al., 1987) which was more pronounced in the temporal-parietal than in the frontal regions. Contrary to the impairment of the long cortico-cortical pathways, and the damage of subcortical areas, such as basal nucleus of Meynert, the neostriatum is relatively preserved (Leuchter et al., 1992; Perry and Hodges, 1999).

Parkinson's disease

The second group included patients with Parkinson's disease (PD). Since the original description from James Parkinson (Essay on the shaking palsy, 1817), PD is considered mostly as a motor system disorder. The core features of the disease are the expressionless face, poverty and slowness of voluntary movements, resting tremor, stooped posture, axial instability, rigidity and festinating gait. Neuropathologically PD is characterized by

dopamine depletion in the putamen and in the rostral part of the caudate nucleus (Hornykiewicz and Kish, 1987; Kish et al., 1988), due to an extensive dopaminergic cell loss in the substantia nigra pars compacta. Thus in turn, affects the dopamine levels in the neocortical regions that receive striatal input (DeLong, 1990).

In the last decades neurophysiological, electrophysiological, functional imaging and anatomical studies provided evidence about visuospatial, visual perceptual, visuomotor, and visuo-cognitive impairments, next to other sensory, vegetative and motor dysfunctions. The visual system is affected at several levels, in the retina as well as the visual cortices, which result in an abnormal pattern electroretinogram (Tagliati et al., 1996), primary visual evoked potentials (Bodis-Wollner, 1985; Onofrj et al., 1986; Bandini et al., 2001), color vision (Muller et al., 1999; Diederich et al., 2002), disturbance of contrast sensitivity (Bodis-Wollner et al., 1987; Diederich et al., 2002). A dopaminergic dysregulation of the fronto striatal system in PD leads to apparent higher-level cognitive dysfunctions also (Alexander et al., 1986; Owen et al., 1997; Cools et al., 2002). In PD many ERP studies yielded a delayed latency or decreased amplitude of different cognitive components in both demented and non-demented patients (Stanzione et al., 1991; Tachibana et al., 1992; Miyata et al., 1998; Tachibana et al., 1999; Prabhakar et al., 2000).

Huntington's disease

The third group included patients with Huntington's disease (HD). The clinical manifestations of HD involve a prominent motor dysfunction –chorea- and cognitive deterioration, as well as psychiatric symptoms and personality changes (Purdon et al., 1994; Okun, 2003).

HD is genetically determined autosomal dominant inherited disease. At the gene locus implicated in HD, localized to the short arm of the chromosome 4., there is an excessively long repeat of CAG trinuleotides.

The most striking pathological changes in HD are found within the striatum itself, with the GABA-containing medium-spiny striatal projection neurons bearing the brunt of the pathology. There is a dorsal-to-ventral, anterior-to-posterior and medial-to-lateral progression of cell death, with the dorso-medial striatum affected earliest and the relative

sparing of the ventral striatum and the nucleus accumbens. Striatosomal medium spiny neurons might be affected prior to matrix neurons. The dopaminergic substantia nigra pars compacta, the cholinergic nucleus basalis Meynert, the serotonergic dorsal raphe and the noradrenergic locus ceruleus afferent projection systems appear to be relatively spared (Joel, 2001). Although the striatum suffers the greatest damage, other neuronal regions are affected to varying degree, such as cortex, globus pallidus, subtalamic nucleus, amygdale, thalamus and hypothalamus.

HD related deficits have been reported in tasks assessing a variety of cognitive skills, including episodic memory (Backman et al., 1997), executive functions and planning (Watkins et al., 2000), visuospatial functions (Lawrence et al., 2000; Davis et al., 2003), verbal fluency (Ho et al., 2002). Primary visual evoked potentials are showed to be late and diminished in amplitude in HD (Hennerici et al., 1985; Munte et al., 1997). Latency prolongation of the late cognitive components are also a common finding in the HD literature (Rosenberg et al., 1985; Homberg et al., 1986).

Probabilistic classification learning

Neurobehavioral studies of healthy human subjects, patients with different types of brain lesions, and animal studies have distinguished between explicit (or declarative) and implicit (or non-declarative) memories (Tulving, 1983; Squire and Zola-Morgan, 1991; Reber et al., 1996). Explicit memory reveals to a conscious recollection of previous experiments, with the rememberer's awareness, at the time of the test, of the relation between the current experience and the original encoding. Contrary, the implicit memory is the retrieval of stored information in the absence of the awareness that the current behaviour and experience have been influenced by a particular earlier happening (Schacter, 1992; Squire, 1994; Tulving, 2000). Recently, the probabilistic classification learning (PCL) task has been introduced as a promising tool to investigate implicit learning functions (Knowlton et al., 1994; Knowlton et al., 1996; Reber et al., 1996). In this task subjects are asked whether a specific combination of different geometric forms predict rainy or sunny weather. Each combination is probabilistically related to a particular weather outcome; however the relation is not absolute: in different percentages the combinations are associated with the opposite outcome. During the task individuals

learn gradually which of two outcomes would occur on each trial given the particular combination of cues that appears, although they have no conscious knowledge about the rule.

Recent studies suggest that intact neostriatal functions are necessary for this kind of implicit learning process because subjects with basal ganglia disorders, such as PD and HD and patients with Tourette syndrome had difficulties learning (Knowlton et al., 1996; Reber et al., 1996; Keri et al., 2002a). However, amnesic patients who had damage in the medio-temporal or diencephalic areas showed a normal learning curve in the PCL task, although they were not able to define the meaning of cues explicitly (Knowlton et al., 1996). A recent fMRI study found that during a PCL task multiple brain regions were activated, including bilateral frontal cortices, the occipital cortex and the striatum (Poldrack et al., 1999). The above mentioned studies imply that this kind of learning occurs in the neostriatum or in the prefrontal cortex.

Transcranial direct current stimulation

The aim of our study was to investigate the role of the prefrontal cortex and the striato-frontal circuit on the implicit learning of the PCL task. To achieve this, we have up- or down regulated the excitability of this area using a non-invasive stimulation technique, transcranial direct current stimulation (tDCS). The effectiveness of tDCS has already been proven in animal (Bindman et al., 1964) as well as in human studies (Nitsche and Paulus, 2000; Rosenkranz et al., 2000; Antal et al., 2001; Baudewig et al., 2001; Nitsche and Paulus, 2001). Weak cathodal stimulation, which probably causes membrane hyperpolarization, has been shown to decrease neuronal firing rates and diminish cortical excitability while conversely anodal stimulation enhances it. In humans the amplitude of the TMS induced motor evoked potentials was decreased by cathodal stimulation and was increased by anodal stimulation (Nitsche and Paulus, 2000, 2001). In the visual system Antal et al. has showed that cathodal stimulation of the occipital cortex can decrease the contrast sensitivity (Antal et al., 2001), and the amplitude of the primary visual evoked potential, and increase the threshold of the TMS evoked phosphenes (Antal et al., 2003a). The effects of the tDCS can be detected not only during but after the stimulation also. The after-effects can be prolonged by increasing the current intensity or the duration of

tDCS (Nitsche and Paulus, 2000, 2001). The underlying mechanisms of tDCS-induced neuroplasticity have been related to N-methyl-D-aspartate (NMDA) receptors (Liebetanz et al., 2002). The NMDA-receptor antagonist dextromethorphan suppressed the post-stimulation effects of both anodal and cathodal DC stimulation, in humans.

The aim of the studies

In the following sections I will summarize four of our studies related to the above mentioned topics. The first three studies (Antal et al., 2002; Antal et al., 2003b; Antal et al., 2003c) elucidate the neural background of the ultra-rapid semantic categorization by investigating several aspects of the ERP's evoked in the categorization paradigm in different patient groups. In the first study we have concentrated on the differential activity (dN150) evoked by the animal and non-animal pictures in PD. The main aim of the second experiment was to investigate the natural scene categorization in AD and compare the results with those obtained in PD. In the third we wanted to further improve our understanding about the role of the cortico-striatal circuits in the categorization process by examining HD patients. The fourth study (Kincses et al., 2004) was dedicated to shade light on the role of the fronto-striatal network in the implicit learning and classification.

Methods

Categorization task

Subjects

All the subjects fulfilled the following criteria: clear ocular media, normal intraocular pressure, no history of diabetes, alcoholism or mental deterioration, and visual acuity better than 0.9 with or without correction. All of the subjects gave informed consents according to the Declaration of Helsinki (BMJ 1991; 302: 1194).

First study

The study included 45 participants. Twenty-five PD patients (14 males, 11 females) in the age range of 42–75 years (mean: 63.8, SD = 9.3) were tested. The average duration of PD was 59 months (range: 10–120, SD = 42), the mean Hoehn & Yahr stage was 2.1 (SD = 0.5) (Hoehn and Yahr, 1967). The mean Unified Parkinson's Disease Rating Scale (UPDRS) total score was 30.6 (range: 5–74, SD = 17.5) (Fahn and Elton, 1987). The mean score in the Activity of Daily Living (ADL) scale was 89.4 % (range: 70–100, SD = 8.2) (Schwab and England, 1969). The mean score in the Mini-Mental State Examination (MMSE) was 28.0 (range: 24–30, SD = 2.0) (Folstein et al., 1975). The mean level of education was 11.2 years (range: 8–18, SD = 2.8). Twenty-one patients were on dopaminergic and/or anticholinergic therapy. Seventeen patients were receiving L-dopa (mean dose: 524 mg/day, range: 200–1000, SD = 234), and 10 patients were receiving the MAO-B inhibitor selegiline (each of them 10 mg/day). Seven PD subjects were on the anticholinergic drug procyclidine (mean dose 11.0 mg/day, range: 7.5–15, SD = 2.8). All patients were in on-phase. SPECT and MRI scans were performed in order to exclude cerebral pathologies. The control group comprised 20 healthy volunteers (8 males, 12 females) who were recruited from the university staff and their relatives. Their age ranged between 40 and 74 years (mean: 59.7, SD = 11.1). The mean score in the MMSE was 29.3 (range: 27–30, SD = 1.1) (Farina et al., 2000) The mean level of education was 12.2 years (range: 8–18, SD = 3.5).

Second study

The study included 63 participants. Twenty AD patients (12 males, 8 females) in the age range of 54-79 years (mean: 68.8) were tested. The average duration of AD was 22.1 months (range: 8-32). The mean score in the MMSE) was 22.0 (range: 14-29, SD=3.6). The mean level of education was 12.8 years (range: 8-18, SD=3.6). The diagnosis of probable AD was based on the DSM-IV criteria (American Psychiatrics Association, 1994). Fifteen subjects were receiving cholinesterase inhibitor (10 subjects were on Aricept, mean dose: 7.5 mg/day, range: 5-10 mg, SD=1.7; 5 subjects were on Exelon, mean dose: 4.2 mg/day, range: 3-6 mg, SD=1.5).

Twenty-three PD patients (15 males, 8 females) in the age range of 57-75 years (mean: 67.6) were tested. The average duration of PD was 52 months (range: 15-110), the mean Hoehn & Yahr stage was 2.0 (range: 1-3, SD=0.5). The mean UPDRS total score was 29.9 (range: 5-69, SD=15.5) (10). The mean score in the ADL scale was 89.8 % (range: 70-100, SD=7.7). The mean score in the MMSE was 27.8 (range: 24-30, SD=1.8). The mean level of education was 11.1 years (range: 8-18, SD=3.1). Twenty patients were on dopaminergic and/or anticholinergic therapy. Thirteen patients were receiving L-dopa (mean dose: 546 mg/day, range: 200-1000, SD=247), and 6 patients were receiving the MAO-B inhibitor selegiline (each of them 10 mg/day). Seven PD subjects were on the anticholinergic drug procyclidine (mean dose 11.0 mg/day, range: 7.5-15, SD= 2.8).

The control group comprised 20 healthy volunteers (15 males, 5 females) who were recruited from the university staff and their relatives. Their age ranged between 52 and 74 years (mean: 64.25, SD=8.0). The mean score in the MMSE was 29.1 (range: 27-30, SD=0.9). The mean level of education was 11.3 years (range: 8-18, SD=2.9).

Third study

Nine HD patients (7 males and 2 females) in the age range of 180 28–60 years (mean 48.66, SD 11.9 years) and 6 nonsymptomatic HDC subjects (4 males and 2 females) in the age range of 27–52 years (mean=37.83, SD:=9.66 years) were tested. All the subjects in the HD group showed typical cognitive and motor symptoms. In both the HD group and in the HDC group, all the subjects had an extension of the CAG trinucleotide repeat, as shown by polymerase chain reaction. The average duration (from the onset of the first symptoms) of HD was 7.87 years (range=1–14, SD=4.73 years). The mean CAG repeat was 45.33 (range 40–51, SD 3.2) in the HD group and 43.33 (range=41–45, SD=1.4) in the HDC subjects. The mean score in the MMSE was 22.7 (range=18–24, SD=2.4) in the HC group and 29.2 (range=28–30, SD=1.1) in the HDC group. The control group comprised 14 healthy volunteers (9 males and 5 females) who were recruited from the university staff and their relatives. Their age ranged between 30 and 60 years (mean=44.2, SD=8.3years). The mean score in the MMSE was 29.6 (range=28–30, SD=1.1) There were no significant differences between control and HD and HDC subjects concerning their age and education level (p=1 0.05). None of the control subjects

were taking CNS-active medications that were clinically thought to contribute to the cognitive dysfunction. Demographical data of the subjects are showed in Table 1.

	HC	HDC	C
m/f	7/2	4/2	9/5
Age (years)	48.66±11.9	37.83±9.7	44.2±8.3
Dur. of dis.(years)	7.87±4.73	--	--
CAG repeat	45.33±3.2	43.33±1.4	--
MMSE	22.7±2.4	29.2±1.1	29.6±1.1
Education (years)	12.0±4.1	14.0±2.8	14.0±6.2

Table 1.

Demographical data of the subjects from the third study.

Stimuli

The stimulus battery included approximately 3000 color photographs of complex natural images, containing either an animal or a non-animal item. All stimuli were available from commercial databases and were matched for average luminance. Animals included birds, mammals, reptiles, sea creatures, and insects. Non-animals were pictures of mountains, forests, rivers, lakes, buildings, flowers, fruits, and urban scenes with people, vehicles, and other artificial objects. All stimuli subtended a vertical visual angle of 10 degrees and a horizontal visual angle of 15 degrees from a viewing distance of 1 m. A small fixation dot was present in the middle of the video screen (Studioworks 57i), controlled by an IBM compatible Pentium PC. The luminance of the stimulus area (80cd/m2) and the background luminance (8cd/m2) were held constant throughout the experiment.

Procedure

Participants were asked to fixate on the small dot in the middle of the screen. The sequence of trials was initiated by the subject by pressing one of the two response buttons. The first trial began 2 s after the initiating response. One trial consisted of the

presentation of a single stimulus for 30 ms. Subjects were asked to decide whether the presented image contained an animal (target) or a non-animal (distractor) item with pressing the appropriate button within 1500 ms. The inter-stimulus interval was 2 s. Stimuli were presented in a randomized order. The probabilities of target and distractor items were equal (50%). The task consisted of 500 trials in two separate blocks of 250. No images were presented twice in order to avoid practice effects. A training block was given before the test to ensure that each subject understood the task.

Electrophysiological recordings

For the electrophysiological recordings, gold cup electrodes with a diameter of 6 mm were used, which were placed in accordance with the international 10-20 system. The primary evoked potential was recorded at Oz referred to an electrode positioned to 70% between the distance of inion and nasion. ERPs were recorded at Fz, Cz, Pz, F3, F4, T3, and T4 referred to linked mastoids (Rlm). The ground electrode was located on the forehead. Signals were amplified 10,000 times. Data were collected and analyzed off-line by an IBM-compatible PC. Filters were set at 0.1 high-pass and 70 Hz low-pass. Notch filter was used to remove 50 Hz interferences. The sampling rate was 1,000 Hz. Individual potentials were baseline corrected on the basis of a 100 ms prestimulus period. The analysis time of poststimulus period was 850 ms. In order to control eye movements, a concurrent electrooculogram (EOG) was recorded. Automatic artifact rejection was applied to remove trials with blinks and other artifacts.

Data analysis

N1 was the major negative deflection on the ERP between 150 and 300 ms following the stimulus onset. The two potential curves were subtracted from each other point by point and the differential activity concerning to the N1 wave was called dN150. To test the normality of distribution, data were entered into Kolgomorov-Smirnov analyses. Mean amplitudes and peak latencies were treated with repeated measures analyses of variance (ANOVAs). For post hoc comparisons, Tukey's HSD test were used. To control the type II errors, Greenhouse-Geisser corrections were included. All ANOVA were repeated with

medication doses as covariants. Differences in behavioral measures were analyzed with Mann-Whithney U test.

Implicit learning task

Subjects

The study involved 22 subjects (mean age= 28.2 years, range= 21-43, SD= 5.2, 12 men) fulfilling the following criteria: visual acuity better than 0.9 with or without correction and no metallic implants or electrical devices. All of the subjects gave their informed consent and the Ethics Committee of University of Göttingen approved the study.

Stimuli and procedure

Stimuli were four different geometrical shapes presented on a computer screen in one row (Figure 1.). Each stimulus had 120 pixel height and 120 pixel width. In a given trial, a stimulus consisted of one, two or three geometrical forms. The exposure time of cues was 1000 ms. On each trial, subjects were asked whether the given combination of geometrical forms meant rainy or sunny weather by pushing one of the two mouse buttons. After the subject's response, the correct answer was presented together with a pictogram of the weather. The inter-stimulus interval (ISI) was 1000ms. The four cues were associated with the outcome sunshine either in 75, 57, 43 or 25%, and thus either 25, 43, 57 or 75% with rain. Table 1 shows the frequency and probabilities of the different combinations. Fifty trials were presented in five blocks (ten trials each). Before the test, a brief practice session was given to all subjects to be sure that all subjects understood and were able to perform the task. The stimuli used in the practice session were not included in the PLC task. Every subject was tested 3 times (no current, anodal and cathodal stimulation) with at least one week break. The frequency values that indicated how many times the given geometric forms meant rain or sunshine were changed between the sessions, and were randomized among subjects.

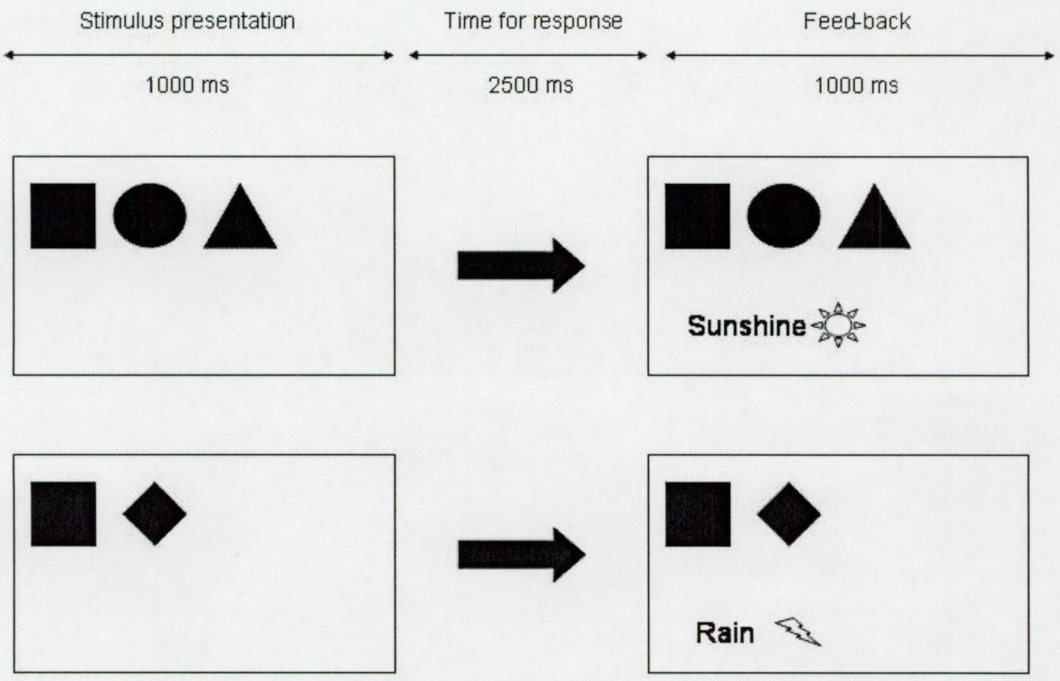

Figure 1.

Appearance of the computer screen at the beginning of a given trial. After the presentation of a stimulus (a given combination of the four geometric forms) the subjects has to decide whether the stimulus predicts sunny or rainy weather. After pushing one of the mouse buttons, the correct answer is provided.

Cue	Frequency	Sunshine	Rain	*P* (Sun)
■, ▲	4	4	0	1.00
■, ▲, ●	1	1	0	1.00
■	7	6	1	0.86
■, ●	4	3	1	0.75
▲	5	3	2	0.60
■, ◆	2	1	1	0.50
▲, ●	2	1	1	0.50
■, ●, ◆	2	1	1	0.50
■, ▲, ◆	2	1	1	0.50
●	5	2	3	0.40
▲, ◆	4	1	3	0.25
◆	7	1	6	0.14
▲, ●, ◆	1	0	1	0.00
●, ◆	4	0	4	0.00
Total	50	25	25	

Table 2.

Probabilistic structure of category cues. Frequency values show how many times a stimulus occurred during the test. "Sunshine" and "rain" denote how frequently a stimulus indicated sunny or rainy weather. P (Sun) is the probability that the weather outcome was sunny for a given stimulus.

tDCS stimulation

tDCS was delivered by a battery driven, constant current stimulator using a pair of electrodes in 5 x 7 cm pieces of water-soaked synthetic sponge. Two electrode montages were used: the first electrode was placed over the primary occipital cortex (Oz) or over the left PFC (Fp3) and the polarity referred to Cz. The left prefrontal stimulation was chosen based on previous neuroimaging studies providing evidence that in different kinds of implicit memory tests (lexical as well as non-lexical) the left PFC is activated (Raichle et al., 1994; Demb et al., 1995; Wagner et al., 1997; Buckner et al., 1998). Besides this, Strafella et al. (2001) demonstrated that repetitive transcranial magnetic stimulation (rTMS) of the left PFC induced dopamine release in the ipsilateral caudate nucleus (Strafella et al., 2001). We did not stimulate both cortical areas because due to the stimulation technique we use only a space-limited cortical area can be stimulated with a given current strength. Stimulating both areas simultaneously would have exceeded these limits.

Fourteen subjects were tested using the first, while 8 subjects were tested using the second electrode montage. The current was applied for 10 minutes with an intensity of 1.0 mA. After five minutes of stimulation, the task was initiated and the fifth block was completed exactly after the tenth minute of stimulation. Constant current flow was controlled by a voltmeter. Anodal and cathodal stimulations were randomized among subjects.

Results

Categorization tasks

First study

Behavioral measures

The average proportion of correct category-responses was 94.3% for the control subjects (range: 88–100) and 91.8% for the PD patients (range: 80–100). There was no significant difference between the two groups. The mean reaction time (RT) for the controls was 589.7 ms (range: 428–731), while that was 668.4ms for the patients (range: 498–800). The RTs in both groups were longer for non-animal stimuli. The RTs did not correlate with amplitude and latency values of the ERP components ($r < 0.2$) and with the MMSE scores ($r < 0.25$). There was a significant difference between the RTs of the two groups ($p < 0.05$).

ERP amplitudes

For the N1 component, there were main effects of stimulus ($F(1,43) = 51.29$, $p < 0.0001$; $e = 0.811$) and electrode site ($F(6,258) = 5.37$, $p < 0.0001$; $e = 0.811$). Interactions between group and stimulus ($F(1,43) = 15.45$, $p < 0.001$), group and electrode site ($F(6,258) = 3.28$, $p < 0.01$), and stimulus and electrode site ($F(6,258) = 4.12$, $p < 0.001$) were also significant. The main effect of group ($p > 0.11$) and the 3-way interaction ($p > 0.15$) remained non-significant.

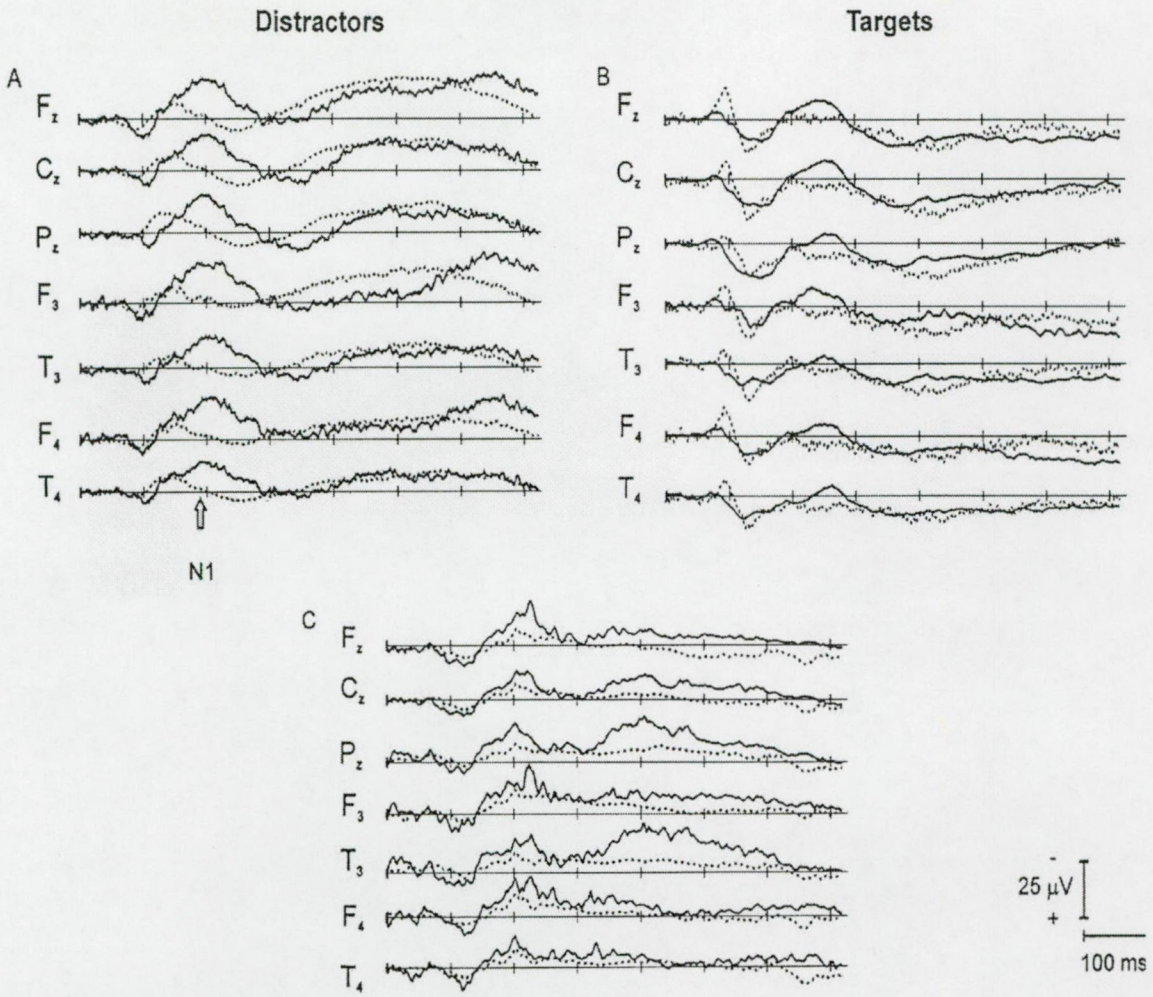

Figure 2.

Grand averaged potentials for A distractor (non-animal) and for B target (animal) stimuli in the control group (continuous line) and in the PD group (dotted line). C Differential curves between non-animal and animal responses.

Tukey's HSD tests revealed that non-animals elicited more negative responses than animals at each electrode position with the exception of T4 ($p = 0.07$). Within-group comparisons indicated that these more negative non-animal components were present only in the control group ($p < 0.001$). In the PD group, animal and non-animal scenes elicited highly similar N1 waves. Considering the results of between-group comparisons, there was no significant difference between the controls and PD patients in the case of animal scenes. In contrast, non-animal stimuli evoked a less pronounced negativity in the PD group in comparison with the controls ($p < 0.001$) (Figure 3., Table 2.).

	Distractors/non-animals images		Target/animal images	
	controls	PD patients	controls	PD patients
Fz	-5.4 (3.6)	-3.2 (2.2)**	-3.6 (3.2)	-2.5 (1.8)**
Cz	-5.2 (4.0)	-2.6 (1.6)**	-3.5 (2.7)	-1.9 (1.7)**
Pz	-4.0 (3.4)	-2.5 (1.6)**	-2.7 (2.8)	-2.1 (1.8)
F3	-4.6 (3.3)	-3.0 (1.6)**	-2.9 (2.7)	-2.4 (1.6)
T3	-4.2 (3.1)	-3.0 (1.9)**	-2.9 (2.7)	-2.6 (1.8)
F4	-4.3 (3.0)	-2.5 (1.8)**	-2.4 (2.4)	-2.2 (1.7)
T4	-3.9 (2.8)	-2.3 (1.6)	-2.8 (2.0)	-2.4 (1.7)

Table 3.

*Mean ERP amplitudes in the control subjects and Parkinson's disease patients. Mean amplitudes (μV) and standard deviations for distractor and target trials in three time-windows. Stars indicate significant between-group differences (Tukey's HSD test, **p<0.005, *p<0.05).*

ERP latencies

The same ANOVAs as in the amplitude analyses were conducted on peak latencies. For the N1 component, there was no significant difference between the two groups.

Medication effects, and gender differences

Medications types (L-Dopa, Procyclidine, Selegiline) and L-Dopa doses were included in the above-described ANOVAs as covariates. These analyses revealed negative results ($F < 1.94$; $p > 0.05$). The statistical analysis (separate ANOVAs) including three treatment subgroups (L-Dopa, Selegiline, Procyclidine) also resulted in non-significant outcomes ($F < 2.6$; $p > 0.05$). Finally, we found no significant differences between men and women ($F = 0.48$; $p > 0.1$).

Second study

Behavioral measures

The average proportion of correct category-responses was 93.5% for the control subjects (range: 88-100), 88.0% for the AD patients (range: 68-96), and 90,4 % for the PD patients (range: 80-98). There was a significant difference between the control and the AD patients ($p< 0.05$). The mean reaction time was 599.7 ms for the controls (range: 428-731), 638.6 ms for the AD patients (range: 568-700), and 667.0 ms for the PD patients (range: 510-800). There was a significant difference between the reaction time of the control and PD groups ($p<0.05$).

Mean amplitude of dN150: controls vs. PD patients

Figure 4 shows grand averaged potentials and differential curves obtained from the control subjects, PD, and AD patients. Figure 5 demonstrates the mean amplitudes. After the practice trial, the trial-to-trial variabilities were about the same in all groups. The ANOVA conducted on the mean amplitude values revealed a significant between-group difference ($F(1,41)=6.22$, $p<0.02$). Main effects of stimulus and recording site were also significant ($F(1,41)=10.42$, $p<0.005$ and $F(6,246)=5.84$, $p<0.0001$, respectively). Further, there was a significant interactions between group and stimulus type ($F(1,41)=8.28$, $p<0.01$), and group and recording site ($F(6,246)=7.16$, $p<0.0001$). Tukey's HSD tests indicated that in the control group non-animals elicited more negative responses than animals at each recording site ($p<0.001$), whereas in the PD group animal and non-animal stimuli evoked early negativities with similar amplitudes. In the control group, there was a definitely deep negativity at the left temporal recording site (T3), which was more pronounced in the non-animal condition, that is, more negative in comparison with the amplitudes measured at Pz, F3, F4, T4 ($p<0.01$). At the same time, the PD patients exhibited highly homogeneous amplitudes at each recording site without significant differences. Finally, according to the post hoc between group comparisons, animal responses were similar in both the control and PD groups. In contrast, non-animal potentials were less negative in the PD group than in the control group with the exception of T4 ($p<0.001$). This latter result confirms and further specifies the significant group by

stimulus interaction. Finally, when L-dopa and procyclidine doses were included as covariants, the results remained unchanged.

Mean amplitude of dN150: controls vs. AD patients

The three-way ANOVA indicated only two main effects; for stimulus ($F(1,38)=24.90$ $p<0.0001$) and recording sites ($F(6,228)=8.72$, $p<0.0001$). Critically, the main effect of group and the group by stimulus interaction remained non-significant ($F<2$, $p>0.2$), demonstrating that the AD patients did not differ from the controls and a PD-like differential impairment for non-animals was not present (Figure 4, 5).

Mean amplitude of dN150: AD vs. PD patients

When the patient groups were compared with a separate three-way ANOVA, a tendency for group was observed ($F(1,41)=3.14$, $p=0.08$). There were main effects of stimulus and recording site ($F(1,41)=13.90$, $p<0.001$ and $F(6,246)=2.86$, $p<0.02$, respectively). The group by stimulus and the group by recording site interactions also reached the level of statistical significance ($F(1,41)=9.63$, $p<0.005$ and $F(6,246)=2.86$, $p<0.002$, respectively). In the AD group, non-animals elicited more negative potentials at Pz, T3, F4 ($p<0.005$) and similar tendencies were present at Fz ($p=0.17$), Cz ($p=0.11$), and F3 ($p=0.08$). The AD patients exhibited more negative non-animals potentials in comparison with that of the PD patients at Fz, Cz ($p<0.001$), T3 ($p<0.0001$), and F4 ($p<0.05$). Tendencies towards the same direction were observable at Pz ($p=0.15$) and F3 ($p=0.16$) (Figure 4, 5).

Peak latency

As indicated by main effects of group, both the PD and AD patients displayed delayed N150 components in comparison with that of the controls ($F(1,41)=6.47$, $p<0.02$ and $F(1,38)=12.81$, $p<0.002$, respectively). N150 latency did not differentiate between the PD and AD patients (Figure 6.). In the case of PD vs. controls comparison, the effect of recording sites was significant, but when Greenhouse-Geisser correction was included only a tendency remained ($p=0.09$, $\varepsilon=0.262$). The group by recording sites interaction was significant ($F(6,246)=4.26$, $p<0.0005$). For the AD vs. controls comparison, there was a significant effect of recording site ($F(6,228)=3.02$, $p<0.01$). In general, post hoc

comparisons revealed that both the PD and AD patients had delayed peak latencies in comparison with the controls and this effect was present at each recording site ($p<0.001$).

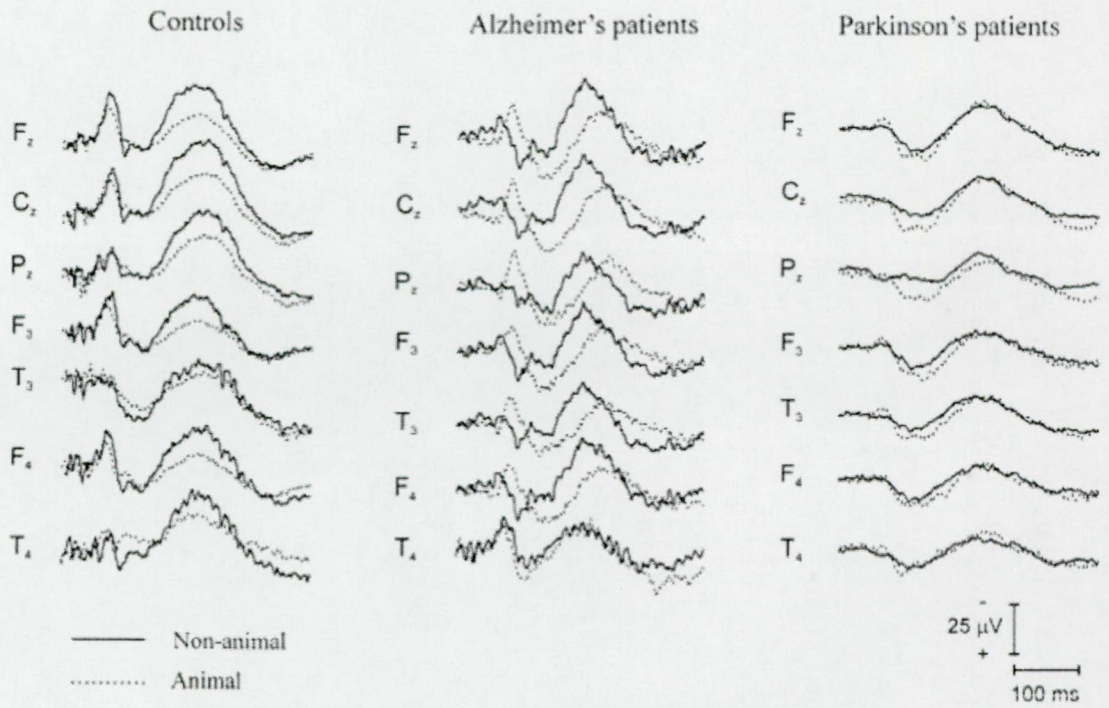

Figure 3.

The figure shows grand averaged potentials for non-animal/ distractor (continuous line) and for animal/ target stimuli (dotted line) in the control, in the AD and in the PD group.

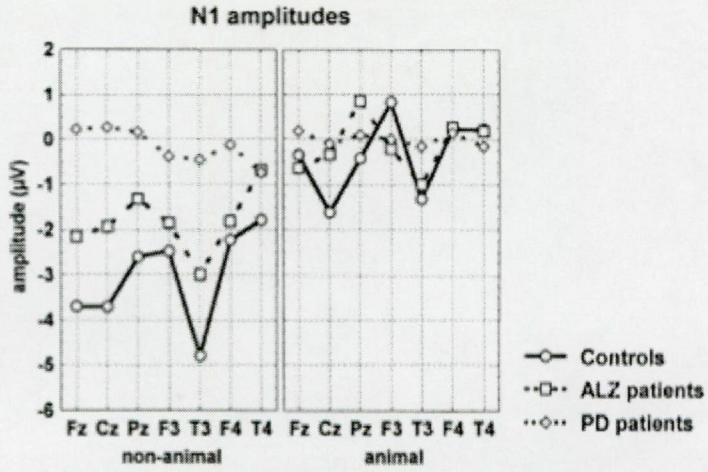

Figure 4.

The figure shows mean amplitude values of the non-animal/distractor trials and animal/ target trials from the controls, from the AD and from the PD groups.

Third study

Concerning the primary occipital component (P100), there was no significant difference between the control subjects and the HD patients ($p > 0.1$; table 2.). However, the amplitude of the N1 component was smaller for both kinds of stimuli in the HD group than in the control and in the HDC groups (Figure 7.). Comparing the control and the HD groups, there were main effects of stimulus ($F(1, 22) = 5.63$, $p < 0.03$, $e = 1.00$) and electrode site ($F(6, 132) = 13.3$, $p < 0.0001$, $e = 0.495$). The effect of group almost reached the significance level ($F(1, 22) = 4.05$, $p = 0.056$). The interactions between group and electrode site ($F(6, 132) = 4.604$, $p < 0.003$, $e = 0.495$) were also significant. Other two-way interactions remained non-significant (group and stimulus: $p = 0.56$; stimulus and electrode site: $p = 0.14$). The three-way interaction was almost significant ($F(6, 132) = 2.03$, $p = 0.06$, $e = 0.61$). Fisher's LSD tests revealed that non-animal items elicited more negative responses than animal items at each electrode site ($p < 0.015$). Within-group comparisons indicated that these more negative non-animal components only were present in the control group at all electrode locations ($p < 0.0001$). Conversely, in the HD group, the non-animal items failed to trigger a more negative component at the

two temporal sites (T3 and T4, $p = 0.68$); at all other electrode sites the non-animal components were more negative than the animal components ($p < 0.05$; Figure 8). Comparing the control and the HDC groups, the three-way ANOVA showed main effects of stimulus ($F(1, 19) = 17.056$, $p < 0.0006$) and electrode localization ($F(6, 114) = 9.37$, $p < 0.0001$, $e = 0.48$). The other effects and interactions remained non-significant. The CAG repeat length and the duration of the disease did not correlate with the amplitude of the N1 component (Spearman $r = -0.10$ to 0.56 and 0.05–0.3, respectively).

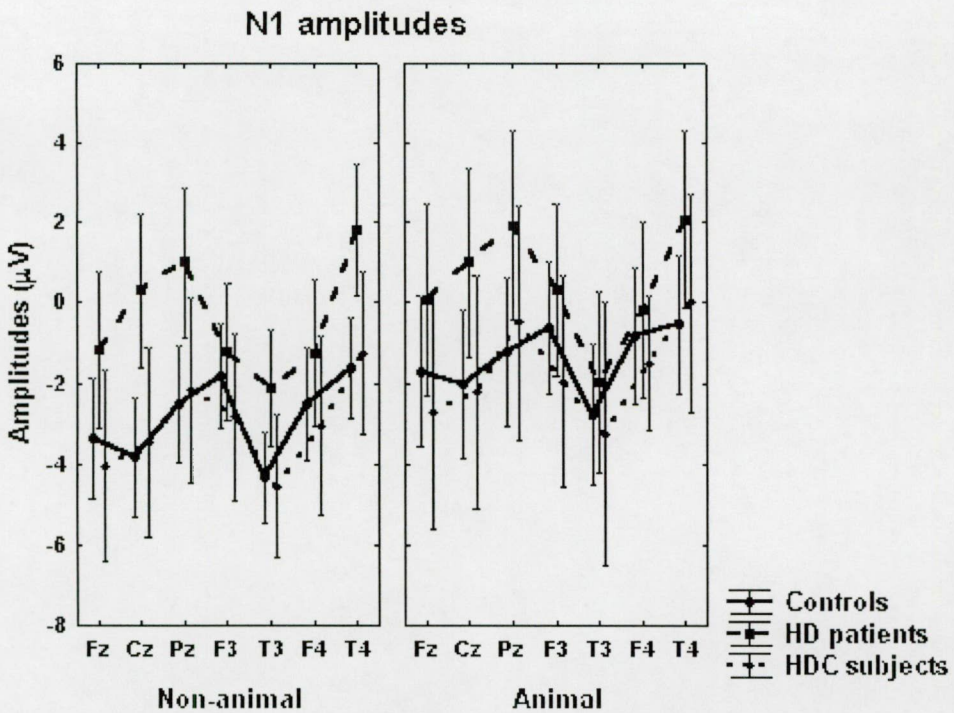

Figure 5.

The figure shows mean amplitude values measured in the 150-250 ms time window of the non-animal/distractor trials and animal/target trials from the control, from the HD and from the HDC groups

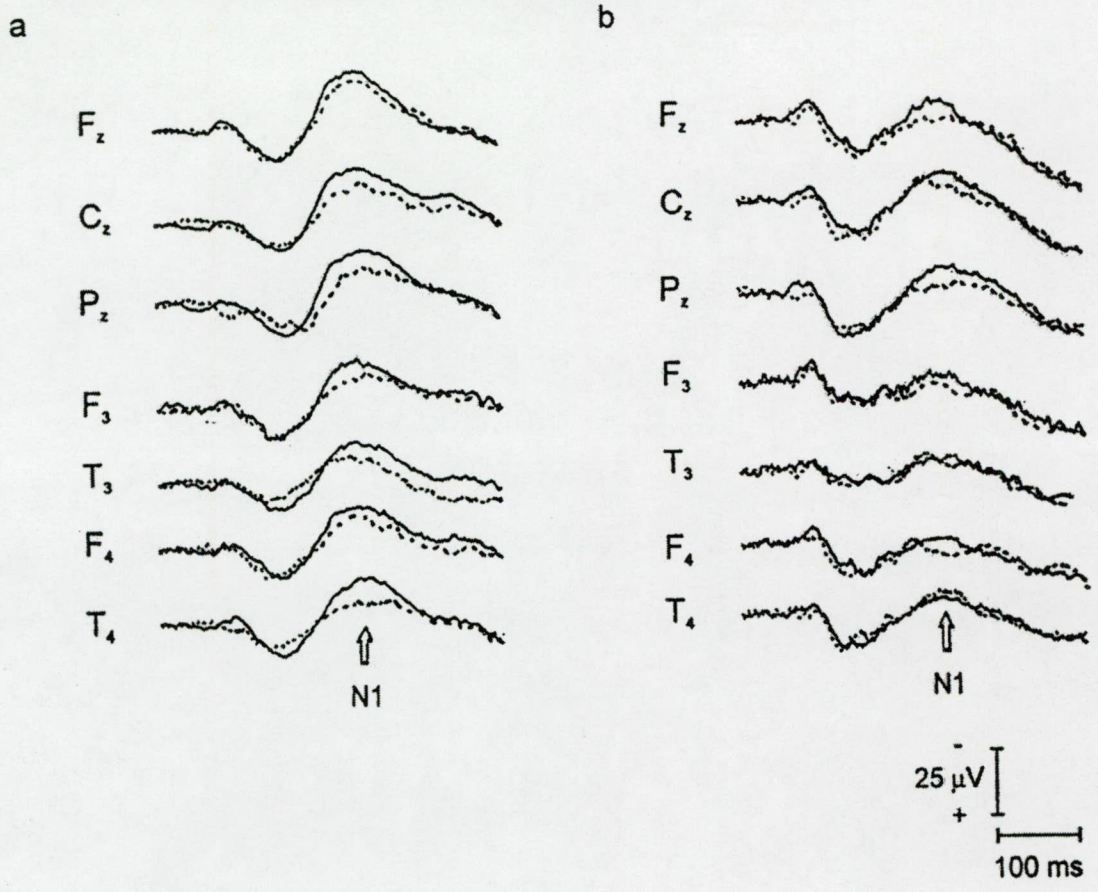

Figure 6.

The figure shows grand averaged potentials for distractor (non-animal - continuous line) and for target (animal - dotted line) stimuli in the control group (a) and in five Huntington's patients (b).

	P100 Ampl. (SD)μV	N1 amplitude difference (μV)						
		Fz	Cz	Pz	F3	F4	T3	T4
Cont.	9.22±5.2	-1.67	-1.82	-1.27	-1.25	-1.58	-1.6984	-1.67
HD	8.58±2.9	-1.25	-0.69	-0.94	-1.06	-1.14	-0.14	-0.27
HDC	10.75±3.2	-1.33	-1.25	-1.66	-0.875	-1.29	-1.54	-1.22

Table 4.

Mean N1 amplitude differences (non-animal/animal) in the control HD and HDC subjects

Implicit learning task

Using the Fp3-Cz electrode montage (N=14), implicit learning was improved by anodal stimulation, while cathodal stimulation had no significant effect. Two-way ANOVA revealed a significant main effect of stimulation ($F(1,13)=5.88$, $p < 0.005$) and trial blocks ($F(4,52)=7.36$, $p < 0.005$). The interaction between stimulation type and trial blocks was not significant ($p > 0.4$). According to Tukey`s HSD test, performance under anodal stimulation was significantly better in the 4th block of trials compared with the first block of anodal stimulation, and compared with the 4th block during cathodal and no stimulation conditions (Figure 2). Cathodal stimulation slightly impaired implicit learning, however the effect was not significant.

Using the Oz-Cz electrode montage (n=8), anodal or cathodal stimulation had no effect. Two way ANOVA revealed only a significant effect of trial blocks ($F(4,28)=3.39$, $p < 0.05$). There was no main effect of stimulation and the interaction between stimulation type and block of trials was also not significant ($p > 0.5$).

Discussion

Categorization tasks

Our results indicate that in PD the animal pictures elicited similar early negativity (N1) as in control subjects, but in case of non-animal images PD patients displayed a less pronounced negativity than controls. In this way the potential difference between the animal and non-animal pictures has disappeared in PD. Although several studies reported early primary visual impairments in PD, like detection of luminance-contrast and hue (Tagliati et al., 1992; Rodnitzky, 1998; Langheinrich et al., 2000; Diederich et al., 2002), the dN150 deficiency is not likely to be the consequence of these early impairments, because the primary evoked potentials (P100) have not differed in this study between groups. The other more satisfactory reason why the disappearance of the dN150 not a simple consequence of primary perceptual impairments is that the potentials evoked by the animal pictures were similar in the experimental groups. These facts together with the negative ophthalmological status, suggest that PD patients have a relatively spared capacities for the early perceptual processing of complex visual images. On the other hand, it is remarkable that in the PD group N1 components for animal and non-animal items were nearly identical. This may point to the deficient mechanisms of early categorization processes.

In contrast, the AD patients, similarly to the healthy controls, exhibited differential responses for the categories. Although their responses were delayed, non-animal items evoked more negative responses in comparison with animals. These results are interesting from the point of view related to the general mental status of the subjects. dN150 was present in demented AD patients with severe clinical symptoms and cognitive decline, while it was absent in non-demented PD patients with much better general cognitive functioning. 16 of the 20 AD patients showed definite recognition difficulties in the Enhanced Cued Recall test, assessing explicit memory, semantic processes and recognition of line drawings of common objects. Despite this, AD subjects scored 88% in the categorization task. Introspective reports from our patients revealed that in many cases they were unable to explicitly identify the animal depicted in the pictures, whereas

they made successful categorization judgments. This strengthens the hypothesis that the categorization was mainly based on weighted selection of relevant features and not on complete object recognitions.

In AD the main feature of the disease is the profound cortical lesions in the association cortices with relatively spared sensory and motor areas; and the disruption of the long cortico-cortical interconnection between those association areas. It is evident from former studies that in AD visual information processing is impaired because of the pathology of cortico-cortical pathways in the ventral occipito-temporal stream (Hof and Bouras, 1991; Hof et al., 1997). In contrast, feature weighting is relatively preserved in AD as reflected by the high categorization performance and the presence of dN150. In PD cortico-cortical pathways are relatively intact, which allows sufficient object recognition functions. At the same time cortico-striatal circuits are impaired, resulting in deficient feature weighting process which may result in the absence of dN150.

Concerning the HD patient group the mean amplitudes were more negative for non-animal scenes as compared with stimuli containing animals at all electrode sites but the lateral temporal electrode sites (T3, T4). Between group comparison demonstrated that the N1 amplitudes were significantly smaller for both kind of stimuli in the HD group in spite of normal primary occipital component (P100). Since several neuroanatomical studies directed attention toward the closed-loop interconnection of the temporal lobe and the striatum (Baizer et al., 1993; Yeterian and Pandya, 1995; Middleton and Strick, 1996), the deficiency in the temporal electrode sites of the early electrical signs of the categorization process probably attributed to the basal ganglia pathology. On the other hand, the general amplitude diminution of the potentials evoked by both kinds of stimuli (see the statistically marginally significant group effect, $p=0.056$) may related to the widespread cortical degeneration that was described in HD.

PD and HD affect the basal ganglia in a very different way. The primary pathological change in PD is the excessive cellular loss in the substantia nigra and the consequent dopamine depletion in the striatum. It is now accepted that these changes leads to an excess of inhibition of the thalamic nuclei via the direct and indirect pathways. In HD the striatum degenerated itself. These pathological changes result in a disinhibition of the

thalamic nuclei via the indirect pathway, and in destroying the lateral inhibition within the striatum, giving a free flow of information through the basal ganglia.

In the light of the above mentioned differences, what can be the role of the basal ganglia in the categorization process? Several animal studies found that in the monkey putamen's and caudatum's cells were not particularly involved in the actual processing of sensory input, but responded to environmental stimuli only in certain contexts which suggest that the striatum is involved in the processes whereby particular responses occur to such stimuli (Rolls et al., 1983; Kimura, 1992). Kimura has reported about sensory responsive putamen neurons in monkeys which showed clear differences in the responses to identical stimuli but presented with different behavioral context (go and no-go conditions) (Kimura, 1992). Similarly the responses of midbrain dopaminergic neurons in monkeys were not of purely sensory nature but were related to the capacity of the stimulus for eliciting behavioral responses. Neurons were responsive for both go and no-go stimuli but responses were enhanced when stimuli elicited limb movement in go trials. These neurons had surprisingly short reaction latency. The median onset latency was 85 and 95 ms for go and no-go trials respectively and the responses peaking around 130, 140 ms (Schultz and Romo, 1990). In this study the presence of responses in individual trials lacking hand or eye movements suggest that dopaminergic neurons in the midbrain do not trigger the behavioral reaction. Rather, impulses of the neurons would inform postsynaptic structures about the presence of a stimulus associated with the availability of an object of high interest. In this way these structures are providing an initial input to neuronal systems subserving goal-directed functions.

Kropotov et al. recorded impulse activity of the neurons in the human basal ganglia–thalamocortical circuits (Kropotov and Etlinger, 1999). Those recordings showed similar short response latencies in human as was reported earlier in monkeys (~100ms). They found that these subcortical circuits are involved in the process of selection of an appropriate sensory stimulus for advanced processing and in selection of an appropriate motor action. They observed that in the no-go condition some thalamic neurons exhibited inhibition of activity following the sensory related activation. This inhibition was associated with a negative deflection in the depth ERPs. They argued that this negativity can be a counterpart of the scalp recorded, frontally distributed no-go component reported

by other studies (Jodo and Kayama, 1992; Jackson et al., 1999). These studies are in line with our results. The lack of differential activation in PD can be explained by the malfunctioning of the above mentioned basal ganglia thalamo-cortical pathways. Due to the dopamine depletion the relevant structures may not give a differential input to other parts of the categorization network, which can result in the lack of the early, categorization-related electrophysiological signs. Additionally Kropotov et al. found evidence that, cells in these subcortical circuits showed different discharge rates when subjects were asked to draw attention on the different features of the objects (shape, orientation, luminosity). Indeed, when subject are informed that they are requested to distinguish between animal and non-animal items they tend to focus on critical features that can ease decision making (Kropotov and Etlinger, 1999). This top-down attentional bias, probably mediated by fronto-striatal circuits, can facilitate object categorization by feature weighting (Humphreys et al., 1989; Abdullaev and Melnichuk, 1997).

The question still remains that what is the special role of the different parts of the basal ganglia thalamo-cortical network in this process. The fact that in HD the dN150 is relatively spared comparing to PD, suggests that the indirect pathway which is primarily damaged in HD may play a smaller role in the early categorization, but the direct pathway, impaired in PD is a crucial component of those processes. Another possibility why we have not seen such prominent changes in HD is that with the progression of the disease different part of the striatum is affected. Our HD group contained symptomatic patients with a quite wide range of disease duration. It is possible that in a bigger patient group we could detect different electrophysiological sign in the different stages of the disease. On the other hand, the lack of correlation between the duration of the disease and the amplitude of the dN150 argues against this hypothesis.

Implicit learning task

Neurobehavioral studies of humans and experimental animals with selective lesions distinguished between a kind of memory dependent on medial temporal lobe and diencephalic structures (declarative memory) and various other kinds of (non-declarative) memory that are independent of these structures. Whereas declarative (or explicit) memory affords the capacity for conscious recollection about facts and events, non-

declarative (or implicit) memory does not appear to require awareness of any memory content. On the other hand, declarative memory is considered to support the flexible use of stored knowledge so that the task knowledge can be used in situations different from original learning context. Non-declarative memory, in contrast, has been considered to be more closely tied to the original learning situation and less accessible to other systems. Several brain regions were reported to be involved in implicit memory processes, but the vast majority of the studies pointed out the striato-frontal network as a major candidate of the unconscious knowledge acquiring during different kind of implicit memory tasks. Implicit learning of visuomotor sequences was impaired in patients with PFC lesions, independently of the side and size of the lesions (Gomez Beldarrain et al., 2002). TMS over the dorsolateral PFC also selectively impaired implicit learning of a sequence on the serial reaction time task (Pascual-Leone et al., 1996). Using repetitive TMS, an impairment of learning abstract patterns was found by stimulating the right dorsolateral PFC (Epstein et al., 2002) while it was shown that stimulation of the left dorsolateral PFC impaired performance in a sequential-letter working memory task (Mull and Seyal, 2001). PET studies indicated the deactivation of left PFC during semantic priming (for a review see: (Gabrieli et al., 1998)). On the other hand patients with PD and HD disease and Tourette syndrome were found to be impaired in implicit learning tasks.

Recent studies support the possibility that PFC is involved in implicit learning processes, mainly in the motor domain (Pascual-Leone et al., 1996; Grafton et al., 1998; Sakai et al., 1998; Gomez Beldarrain et al., 2002).

PLC is a useful tool assessing the non-motor implicit learning; with this paradigm we can acquire important information about the underlying neural mechanisms of the non-declarative memory.

PCL was reported to be impaired in PD and HD disease as well as in Tourette syndrome, but was found to be intact in amnestic patients. On the other hand Nuhsman and Deuschl showed that PCL remained unaffected in cerebellar pathology although cerebellum is another important candidate of some kind of implicit learning (Witt et al., 2002).

tDCS seems to be a promising tool to investigate not only the primary sensory functions (Nitsche and Paulus, 2000; Rosenkranz et al., 2000; Antal et al., 2001; Baudewig et al., 2001; Nitsche and Paulus, 2001), but higher level cognitive functions also, as well as the

implicit memory functions (Costain et al., 1964; Lippold and Redfearn, 1964). Recently, it was found that anodal tDCS can modulate implicit motor learning in healthy human subjects while the primary motor cortex was stimulated (Nitsche et al., 2003). In monkeys, Rosen and Stamm (Rosen and Stamm, 1972) found improved learning in a delayed reaction time task stimulating the dorsolateral PFC by anodal stimulation and impaired learning by cathodal stimulation. In our investigation, using the Fp3-Cz electrode montage and 10 minutes stimulation duration, implicit learning was improved by anodal stimulation, while cathodal stimulation had no significant effect. Using Oz-Cz electrode montage neither anodal nor cathodal stimulation had effect. It was suggested by Liebetanz et al. that tDCS probably acts trough some NMDA-receptor dependent mechanisms which resembles some important features of neuroplasticity (Liebetanz et al., 2002). By modulating the firing frequency of the cells, probably can affect the underlying synaptic mechanisms of the learning process.

The induced effects of tDCS we have obtained are probably located intracortically but the PFC and the basal ganglia are so strongly interconnected through several pathways that an alteration of function in either location may have a similar functional effect when a task is used that requires the participation of one or both structures. Indeed, as reported by Strafella et al. repetitive transcranial magnetic stimulation of the human prefrontal cortex induced dopamine release in the caudate nucleus (Strafella et al., 2001).

General discussion

The role of the basal ganglia formation in visual perception and cognition was investigated intensively over the last decades. Indeed, there are some evidences to suggest that the basal ganglia play role in both the complex visual object cognition and visuospatial cognition (Yeterian and Pandya, 1993, 1995). Receiving inputs from the ventral and dorsal stream, sending and receiving information to and from the frontal areas, makes the basal ganglia complex an ideal structure to organize the incoming sensory information on the basis of behavioral requirements which probably stored in the frontal cortex working memory system. In this way the striato-cortical network is an indispensable connecting point of the categorization processes irrespectively of the explicit or implicit nature of the process.

Theoretical argumentations raises the possibility that not only one exclusive implicit or explicit categorization system is active in time (Ashby et al., 1998). These theories assume that the explicit system initially dominates, presumably because it is controlled by consciousness. With training and experience, however, the potential of the implicit system for superior performance often overcomes the initial bias in favor the explicit system. Nevertheless, in most cases, both the explicit and the implicit systems remain active even after learning is complete, and each determines a significant proportion of categorization judgments.

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