

Behavioural aspects of a modified crosstalk between basal ganglia and limbic system in Parkinson's disease

ORSOLYA GYÖRFI¹, HELGA NAGY^{2,3}, MAGDOLNA BOKOR¹ AND SZABOLCS KÉRI^{1,4,5}

¹Nyíró Gyula Hospital – National Institute of Psychiatry and Addiction, Budapest, Hungary

²National Institute of Medical Rehabilitation, Budapest, Hungary,

³Semmelweis University, Department of Neurology, Budapest, Hungary

⁴Budapest University of Technology and Economics, Department of Cognitive Science, Budapest, Hungary

⁵University of Szeged, Institute of Physiology, Szeged, Hungary

Dysfunctions in dopaminergic neurotransmission lead to motor symptoms and cognitive impairments associated with behavioural disturbances. Parkinson's disease is a neurodegenerative disorder which is primarily characterized by an abnormal basal ganglia activity. Recently, increased attention has been directed towards the hippocampus in the development of non-motor symptoms. Given the temporal progression of the disease, dopaminergic depletion firstly affects the dorsal striatum leaving the ventral striatum relatively intact. However, it is possible that the structure and function of the hippocampus shows alterations even in early stages of Parkinson's disease. Subtle cognitive impairments occur in the earliest stages, and therefore Parkinson's disease could provide a unique model to investigate the effect of replacement therapies on a neural network with different baseline dopaminergic levels. Strong evidence suggests that dopaminergic medications improve the motor symptoms, but these medications might have disadvantageous effects on cognitive functions. In this review, we examine the role of dopaminergic changes across several cognitive and behavioural impairments observed in Parkinson's disease, with a special reference to hippocampal dysfunctions.

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THE ROLE OF DOPAMINERGIC NEUROTRANSMISSION IN THE HIPPOCAMPUS

According to traditional trends in the study of human memory, the hippocampus contains the most important and complex neural network. Memory is essential to adaptive behaviour (Euston et al., 2012). To accommodate to extrinsic environmental changes, the organism has to modify stimulus-response dimensions in order to achieve the most flexible behaviour. Neuroplasticity plays a pivotal role in learning, i.e. in the formation and consolidation of memory. The hippocampus is considered as a fundamental example to functional neuroplasticity. It can be characterised by LTP and long-term depression, which are considered as the cellular substrate of learning and memory (Bartish et al., 2015).

Animal experiments demonstrated the dopaminergic modulation of LTP. Electrophysiological studies on rat hippocampal slices provided evidence that D1/D5 agonists enhanced the early phase of LTP in the CA1 hippocampal subregion. According to these results, during tetanic stimulation dopamine enhanced the postsynaptic depolarisation, which is pivotal for LTP induction. The requirement of tetanic stimulation has computational importance in reinforcement learning (Otmakova et al., 1996).

Hamilton et al. (2010) reported similar findings: the induction of high frequency trains of D1 receptors in dentate granule cells activated dendritic voltage-dependent calcium channels, which is another essential physiological activator of dopamine-induced LTP. These experimental models provided evidence that high-frequency dopaminergic activity in the hip-

hippocampus strengthened the synapses which might facilitate reward associated spatial memory formation. The interaction between dopamine firing patterns and information flow provides an insight how the behaviour can be most effectively guided towards the goal to obtain a reward (Grace et al., 2007; Schomaker et al., 2015).

Behavioural studies exploring reward-motivated learning in healthy human subjects highlighted the importance of motivational salience. Learning can be inspired by expecting a provisional re-compensation before the knowledge is perceived. Neuroimaging studies using fMRI paradigms explored the anticipatory mechanisms of reward motivated learning. By using a monetary incentive task, Adcock et al. (2006) found that cues predicting highly-rewarded and later remembered scenes activated the mesolimbic circuit (dopaminergic neurons in the ventral tegmental area, NAc and hippocampus). A positive correlation exists between hippocampal and ventral tegmental area activation, which is associated with long-term memory formation (Adcock et al., 2006).

The relationship behind these behavioural phenomena could be explained by functional anatomical connections between the prefrontal cortex, hippocampus, basal ganglia, and midbrain (ventral tegmental area) dopaminergic systems (Calabresi et al., 2013).

DOPAMINE IN REWARD LEARNING AND NOVELTY SEEKING BEHAVIOUR

Based on electrophysiological studies it is proposed that the mesencephalic dopaminergic system can be divided into two functional components. The first is a slow, tonic release of dopamine, driven by an intrinsic pacemaker that maintains the low tonic concentration. The second is a rapid, brief, high-amplitude phasic release of dopamine that is driven by behaviourally relevant burst firing of dopaminergic neurons. The phasic activity is dependent on afferent inputs and represents a functionally relevant signal to indicate reward and modulate goal-directed behaviour. Phasic changes in the bursting of dopaminergic neurons occur in response to primary or conditioned rewarding stimuli and have been proposed to mediate a prediction error for anticipated rewards (Grace et al., 2007).

The mesencephalic dopaminergic system is interconnected with limbic structures (including the hippocampus, and NAc) and the PFC via two differently directed anatomical links (upward- and downward arc). In this model the NAc plays a pivotal role by integrating the incoming information under the

modulatory influence of the dopamine system. NAc inputs coming from the limbic system and PFC are differentially regulated by dopaminergic receptor subtypes and dopaminergic firing pattern.

Activation of D1 receptors by the high-amplitude phasic dopamine enhances the activity of the downward arc which consists of glutamatergic projections from the hippocampus (subiculum) to the nucleus accumbens, followed by an inhibitory connection to the ventral pallidum, which releases tonic break on the midbrain dopaminergic neurons. This finally results in dopamine release from midbrain dopaminergic neurons (Sesack et al., 2010).

Computational models provided evidence that when the environmental contingencies are rewarding, the dopaminergic neurons fire in a phasic pattern. This pattern via D1-receptor activation enhances the downward arc and maintains the current behaviour to maintain the favourable outcome. A hyperdopaminergic state (a'side effect' of dopamine agonists) in the hippocampus – VTA loop would reciprocally potentiate the subsequent responses, leading to impulsive-compulsive behaviour (Calabresi et al., 2013).

This circuit is also in charge to balance novelty gated information storage. The hippocampus is critical for providing the main novelty signal input to VTA. In turn the VTA releases dopamine that is necessary to stabilise and maintain LTP in the hippocampus (Wittman et al., 2007).

The upward arc consists of a connection from PFC to NAc. Tonic dopaminergic signalling inactivates the prefrontal inputs via D2 receptors, thus enabling the PFC to modulate the behaviour in compelling situations. Behavioural models shows that when the outcome is unfavourable (resulting in punishment), dopaminergic neurons show a tonic firing pattern that inhibits D2 receptors, resulting in PFC activation guiding the shift towards a desirable manner (Calabresi et al., 2013).

It is worthy to highlight the regional contribution of PFC in controlling different aspects of executive functions, thus directing towards a goal-directed behaviour. Summarising several modelling techniques, Szczepanski et al. (2014) assumed that the lateral PFC is critical for selection and manipulation, the medial PFC is responsible for updating, and the role of the orbitofrontal cortex is to assign the social and emotional meaning to goal-directed behaviour.

The clinical data assessing unmedicated PD patients on reward-learning tasks are in accordance with the above mentioned approaches. Results of a longitudinal analysis on newly diagnosed-PD patients

revealed that the unmedicated status correlated with better punishment learning (no tonic dopamine to inactivate the PFC, so they are able to adjust), lower novelty seeking, and impaired performance on reward learning (hypodopaminergic state in VTA-hippocampal loop). Retesting these patients after the initiation of dopaminergic therapy, the results were inverted: the deficits observed in reward learning and novelty seeking were remediated, but the punishment learning was disrupted (Bódi et al., 2009).

The distinct effect of dopaminergic medication on outcome-based learning can be proved as well by comparing PD patients ON and OFF medication. PD patients ON medication were better at learning from negative outcome compared to PD patients in OFF status. The OFF status was related to the avoidance of a previously punishing stimulus ('NoGo' bias), whereas the ON condition was characterized by a higher 'Go' tendency to choose a previously rewarding stimulus (Frank et al., 2004).

DOPAMINERGIC MECHANISMS OF TASK-SWITCHING IN THE STRIATUM

Learning to reverse the responses to a formerly classified stimulus is a cognitive skill that enables to accommodate to current circumstances.

Reversal learning can be assessed using probabilistic reversal tasks. The first step is, called the acquisition phase, when the subject learns to classify the stimuli by several trial-error reinforcements. In the next step the subject should comprehend that the previously learned stimulus is now associated with the opposite response – the participant learns to reverse the choice (Levy-Gigi et al., 2011).

The intact ventral striatum plays a central role in task-switching. This function is affected in PD patients, and the dopaminergic replacement therapy has a discrepant effect on dopaminergic pathways. In early PD, dopamine depletion affects the dorsal striatum, whereas the ventral striatum is relatively intact. Thus, the medication necessary to remedy depleted dopamine levels in the dorsal striatum may 'over-dose' dopamine levels in the relatively intact ventral striatum (MacDonald et al., 2011). Assessing the performance of patients ON and OFF dopaminergic medication, patients ON medication exhibited impaired reversal shifting relative to patients OFF medication (Cools et al., 2006).

A functional imaging study in mild PD patients has strengthened this 'over-dose' hypothesis by confirming that the use of dopaminergic drugs modu-

lates the ventral striatum (NAc), but not the dorsal striatum during the performance of a probabilistic reversal shifting task (Cools et al., 2007).

Another group of investigators found similar impairments of reversal learning in PD patients on dopaminergic medication (Moustafa et al., 2014). They speculated that the learning process, more exactly the reversal phase, is affected. According to this hypothesis, in the beginning of the reversal phase, the subject receives negative feedback, and because of an increase in tonic dopamine function in the PFC, the subject shifts attention to another cue instead of learning to reverse the responses.

BASAL GANGLIA AND HIPPOCAMPUS IN SEQUENCE LEARNING

In learning and memory, the MTL (including the hippocampus) and the basal ganglia have dissociable roles. The MTL is responsible for the establishment of complex associations and integration among multiple stimulus dimensions (episodic memory) and it is important in situations when the stimuli are presented in a novel context. The basal ganglia support feedback-based learning of stimulus-response associations (procedural or habit learning) (Nagy et al., 2007; Shohamy et al., 2009; Dickerson et al., 2015).

Sequence learning, as assessed by the "chaining" task, allows a special insight to evaluate the MTL and BG functions at the same time within the same paradigm. In the "chaining" task, the task is to navigate an animated character – "Kilroy" – through several rooms. The final reward is provided when the animated character leaves the full chain of rooms. In each room, participants must learn the colour of the open door via a trial-error learning process. In the probe phase of the task, subjects had to prove that they learned the correct stimuli in the requested sequential manner. For the right choice, they had to use the context of stimulus-response association (Nagy et al., 2007).

By comparing the results from the "chaining" task between never-medicated PD patients (basal ganglia dysfunction) and a group of patients with amnesic mild cognitive impairment (MTL dysfunction), a behavioural dissociation was found. Never-medicated PD patients had a good performance during the probe phase (preserved contextual learning), but showed impairments in the training phase of the chaining task (dysfunctional sequential learning). aMCI patients completed the task in an opposite manner: they showed intact learning during the sequence

training, but diminished scores on probe phase (dysfunctional context learning) (Nagy et al., 2007).

The distinct roles of basal ganglia and hippocampus in reversal-learning could be assessed using probabilistic reversal classifications tasks. In probabilistic learning, a cue that was initially associated with one outcome 80% of the time will now be associated with another outcome 80% of the time. Reversal involves a successful change of stimulus-response contingency (Shohamy et al., 2009).

Patients with selective hippocampal damage (due to hypoxic brain injury) vs. subjects with basal ganglia dysfunctions (due to Parkinson's disease) performed differently on this task. Both groups were intact at initial learning (guessing correctly the association between a visual cue and the corresponding category) but differed in their reversing features.

Amnesic patients failed to reverse the responses – they tended to perseverate, that is, they used the same cue-response association which was learned before. Interestingly, these patients also displayed mild impairment in neuropsychological tests assessing the frontal functions. These findings suggest that the pathological background resulting in impairment in reversal learning might involve the prefrontal cortex as well (Shohamy et al., 2009).

Instead of reversing the response, PD patients learned and used a new cue-outcome association. This finding is consistent with previous results (Nagy et al., 2007) and also suggests that PD patients are impaired at learning tasks involving the integration of information through multiple cues and trials (Shohamy et al., 2009).

INTRATEMPORAL CHOICE IN BASAL GANGLIA AND HIPPOCAMPUS

The timing of the feedback following the response is another critical point in reward-oriented learning. An optimal learning mechanism should balance between the timing and the subjective magnitude of the reward. These assumptions raise an important question: what pattern is applicable in PD if the feedback is delivered later?

Fourde et al. (2011) proposed a dynamic pattern which involves the hippocampus and the striatum. Patients with a disrupted nigrostriatal system (due to Parkinson's disease) were impaired at learning from immediate feedback in a reinforcement learning task, but not when a delayed feedback was provided. The role of unaffected striatum in immediate response was proved in healthy individuals by functional MRI.

They demonstrated a greater BOLD response in striatum when the feedback was immediate, and in the hippocampus when the feedback was delayed.

Another critical point in goal-oriented learning is the temporal delivery (arrival) of the reward. Increasing attention has been paid to the phenomenon that dopaminergic medications applied for the treatment of PD contribute to development of behavioural addictions, clinically defined as impulsive-compulsive behaviour (Weintraub et al., 2010).

The classification of ICBs shows a great variety of clinical manifestations, including pathological gambling, compulsive shopping, compulsive sexual behaviour, and binge eating. Approximately 13.6% of Parkinson disease patients exhibit ICBs (Voon et al., 2011). An impulsive choice is characterised by a preference for immediately available rewards, even when it is smaller than delayed rewards. The tendency to prefer sooner, smaller but immediate rewards over those that are larger, but temporarily more distant can be quantified with delay discounting tasks (Housden et al., 2010; Napier et al., 2015).

Two possible theories are suggested regarding the development of impulsive-compulsive behaviour. The first assumption postulates that ICB in PD reflects the 'overvaluation' of rewards due to the 'overdosing effect' in the relatively intact ventral striatum. A more accurate explanation is that dopamine in the ventral striatum mediates the incentive salience for the conditioned stimuli, which elicits phasic dopamine firing.

The second theory describes another mechanism – the delay discounting – which might contribute to the appearance of impulsive-compulsive behaviour (Housden et al., 2010). Comparing the effect of incentive salience (reinforced reward) and delay discounting in the development of ICB in PD patients, the 'overestimation' hypothesis seems to be incorrect. PD patients with ICB exhibited similar scores as the healthy control group on a reward learning task. However these scores were higher than the scores of PD patients without ICB, which contradicts the 'overestimation' theory (Housden et al., 2010).

A study conducted by Voon et al. (2010) found a greater impulsive choice in PD patients with medication-related ICBs. By implementing a feedback-based intratemporal choice task, they demonstrated that the PD patients with ICB on dopaminergic medication associated an increased impulsive choice compared with PD patients without ICB (Voon et al., 2010).

There is also a genetic association that may be uniquely associated with delay discounting in PD. It has been identified that SNCA gene duplication

carriers with PD exhibited increased impulsivity indicated by elevated delay discounting for reward (Szamosi et al., 2013).

Evidence from animal models demonstrated that the hippocampus has an important role to decide between an immediate-smaller or delayed-larger reward. Hippocampus lesioned rats tend to prefer immediate smaller rewards over delayed larger reward (Cheung et al., 2005; McHugh et al., 2008). These findings suggest that the hippocampal system is necessary for tolerating the delayed behavioural choice (Bett et al., 2010).

CONCLUSION

Our review summarised several behavioural dysfunctions resulting from an impaired dopaminergic neurotransmission in the extended basal ganglia – hippocampal system. We also described the pathophysiological background of some cognitive symptoms. PD was considered as a model of altered dopaminergic transmission, assuming that there are distinct baseline neurotransmitter levels in several brain areas.

In clinical practice the beneficial effect of dopaminergic restoration is very well established, but the effect is more complex on non-motor symptoms. Some of the consequences might be favourable, for example when we consider the dopaminergic effect on learning and some affective symptoms. However, medicated PD patients are more attracted to positive outcomes and rewarding stimuli. It is related to changes in personality traits such as novelty seeking and harm avoidance (Bódi et al., 2009).

In contrast, the outcome elicited by dopaminergic replacement therapy might be less favourable regarding impulsive decision making, attenuated cognitive flexibility, and impaired sequence learning. Based on electrophysiological studies, neuroimaging techniques, and clinical evidence it can be concluded that the traditional view of Parkinson's disease as a circumscribed basal ganglia disorder is changing. The main neuropathological hallmark of dopaminergic neural loss also affects the limbic system, including the hippocampal formation.

Currently, extensive data on hippocampal dysfunction in PD are less available, but recent trends in clinical neuroscience indicate that this new direction is promising to better understand the mechanisms of behavioural alterations in PD.

ADDRESS OF CORRESPONDENCE: Orsolya Györfi MD, Nyíró Gyula Hospital – National Institute of Psychiatry and Addiction, Department of Neurology, Lehel utca 59., 1135 Budapest, Hungary. Phone: +36 1 451-2678
E-mail: gyorfio@nyiro-opai.hu

ABBREVIATIONS

aMCI	amnesic mild cognitive impairment
BG	basal ganglia
CA	Cornu Ammonis
DA	dopamine
MRI	magnetic resonance imaging
HC	hippocampus
ICB	impulsive-compulsive behaviour
LTP	long-term potentiation
MTL	medial temporal lobe
NAc	nucleus accumbens
SNCA	alpha synuclein
PD	Parkinson's disease
PFC	prefrontal cortex

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Viselkedési mintázatok vizsgálata a bazális ganglionok és a limbikus rendszer átfedésében

A Parkinson-kóros betegek vizsgálata célszerűnek bizonyul a módosult dopaminerg neurotranszmisszió kognitív jelenségeinek feltérképezésében. A Parkinson-kór a neurodegeneratív betegségek közé tartozik, elsősorban a bazális ganglionok érintettek, habár az utóbbi időben a nem-motoros tünetek hátterének vizsgálata során jelentős figyelem irányul a hippokampuszra is. A betegség neuropatológiai előrehaladását tekintve kezdetben elsősorban a dorzális striátum érintett, míg a ventrális striátum struktúrái megtartottak. Az újabb eredmények felvetik a hippokampusz korai károsodását is. Klinikai szempontból specifikus, enyhe kognitív tünetek már a Parkinson-kór korai stádiumában is megjelenhetnek. Elfogadott tény a szubsztitúciós kezelés kedvező hatása a motoros tünetekre, de a kognitív tünetek esetében ellentmondásos hatásokkal számolhatunk. A betegség neuropatológiai és klinikai jellemzői egy megfelelő modellt kínálnak a terápiaként alkalmazott dopamin-pótlás hatásainak vizsgálatára az eltérő dopaminszinttel rendelkező idegi struktúrák között. Közleményünk célja a bazális ganglionok és limbikus rendszer kapcsolatával foglalkozó vizsgálatok eredményeinek összegzése a kognitív és tanulási mechanizmusok tükrében, különös tekintettel a hippokampuszra.

Kulcsszavak: Parkinson-kór, hippokampusz, dopaminerg neurotranszmisszió, kognitív funkciók