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Impulsivity and Parkinson's disease: More than just disinhibition☆

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Abstract

In the last few years it has become clear that impulsivity is a complex behaviour composed of different domains and dependent on different neural networks. The proposed pathogenetic mechanisms for the emergence of impulsivity disorders in Parkinson's Disease (PD) can be broadly separated into three potentially interacting processes: the contribution of premorbid susceptibility to impulsivity, the contribution of the disease itself to the behaviour and the potential contribution of therapeutic agents. Growing evidence suggests that dopamine and the subthalamic nucleus are playing a certain role in the pathophysiology of different aspects of impulsivity. In this review, we summarise the main concepts defining various components of impulsivity both in healthy subjects and patients affected by PD.

Keywords

Parkinson's disease; Brain imaging; Dopamine; Subthalamic nucleus; Impulsivity; Impulse control disorders

1. Introduction

Impulsivity is a complex personality dimension, which might be defined in different ways. The Diagnostic and Statistical Mental disorders manual-IV RT6 defines impulsivity as "a failure to resist an impulse, drive or temptation to perform an act that is harmful to the person and others". Recent studies have extended beyond the idea of impulsivity being based in poorly planned actions, and have yielded to a broader definition that includes more cognitive functions. In particular, according to Bechara's model [1], two major processes linked to different neural networks and activated by different experimental paradigms have been defined: *motor impulsivity* and *cognitive impulsivity. Motor impulsivity* is described in terms of disinhibition of prepotent responses. *Cognitive impulsivity* [2] is a more complex process, and is the result of a suppression of previously activated cognitive contents [3]. This

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review has two goals: 1) to describe the two different dimensions of impulsivity, focusing on their neural pattern and their specific experimental paradigms 2) to review studies on impulsivity (taking into account the two dimensions) in patients with PD, exploring the role of dopamine replacement therapy (DRT) and the subthalamic nucleus (STN) in the pathophysiology of excessive impulsivity.

2. Cognitive impulsivity

Cognitive impulsivity is a complex psychological domain characterised by different facets.

Altered *decision making* is frequently associated with cognitive impulsivity [1,4,5]. It is the product of an imbalance between two separate, but interacting, neural systems: (1) an impulsive, amygdala-dependent system, which controls immediate and “somatic” behaviour related to a decision and (2) a reflective, prefrontal-dependent system [6], which evaluates the future prospects related to the decision [4]. The conditions that lead to this imbalance include a dysfunctional reflective system and a hyperactive impulsive system [4]. The paradigm most used to measure decision-making is the Iowa Gambling Task (IGT), an ecologically valid decision task involving weighing of immediate rewards against long-term losses. Neuroimaging studies on healthy subjects (HS) showed that the activated regions during IGT were those underlying both somatic activation and future oriented decision-making [7]. However, recent reports showed the complexity of this task that might also be considered as a measure of risk taking [1,8–11]. In particular, poor performance during the first part of the task has been related to ambiguous risk taking [12–15].

Risk taking is considered another facet of cognitive impulsivity [16]. Brand described two kinds of risk taking: risk taking under stable probabilistic contingencies (explicit risk-taking) and ambiguous risk taking, in which the subject is unaware of the probabilistic contingencies [13–15]. Ambiguous risk taking is related to the functioning of the ventral frontostriatal loop [17,18]. In particular, in a recent fMRI study, the neural systems responding to degrees of uncertainty were related to the orbitofrontal cortex and the amygdala, activated in association with the “vigilance”/evaluation-system which responds rapidly to the degree of uncertainty, and to the dorsal striatum that was associated with reward-anticipation [19]. To explore ambiguous risk-taking, researchers have used the Balloon Analogue Risk Task (BART) that involves actual risky behaviour for which riskiness is rewarded up until a point at which further riskiness results in poorer outcomes [20]. The task consists of different trials in which subjects inflate a virtual balloon that can either grow larger or explode [20]. Behavioural studies in HS revealed that poor performance on the BART correlates with high self-reported impulsivity in healthy subjects [20]. So far, only one imaging study has examined neural activation during the BART in HS. In a version of the task adapted for fMRI the authors confirmed the involvement of mesolimbic-frontal pathway during ambiguous active risk-taking [21]. The evaluation of explicit risk-taking may be done by using the Cambridge Gambling Task (CGT) in which the relevant information is presented to the subjects ‘up-front’ and there is no need to learn or retrieve information over consecutive trials. Because of that, the CGT is considered a measure of explicit risk and, compared to the IGT, a way to assess decision-making and risk-taking behaviour outside a learning context [22]. Some data are available on the neuroanatomical correlates of

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performance on the CGT in HS. A modified version of the CGT, the Risk Task [23], has been used in functional imaging studies, revealing significant activations in multiple regions within the inferior and orbital prefrontal cortex, which are involved in the representation of stimulus–reward relationships [24,25].

The *perception of time* and the duration between the choice and the reception of the reward are other crucial factors involved when individuals have to make decisions and consider the outcomes associated with their choices [26]. In this view, when we talk about impulsivity, it's important also to consider the phenomenon of delay discounting, in which a delayed outcome of a choice reduces the subjective value of the reward [27,28]. A way to measure temporal discounting behaviour in human participants experimentally is the Delay Discounting Task (DDT). In delay discounting procedures, participants make choices between rewards that are smaller but sooner versus rewards that are larger but delayed. The temporal discounting pattern has repeatedly been described as following a hyperbolic function, meaning that it is related to a rapid fall of the subjective reward for small delay periods, whereas the decline is slower for longer delay periods [29–31]. Impulsive individuals discount delayed rewards more strongly than do more self-controlled individuals [26]. Strong evidence of limbic and paralimbic cortical activation was found when HS were presented with choices between a smaller earlier reward and a greater but delayed reward [32–34]. Lateral prefrontal and parietal cortices, associated with executive control and time processing itself, were activated when subjects delayed gratification [32–34]. In addition, a study by Tanaka and colleagues [34] suggests that the striatum and the insula might be implicated in the evaluation of reward outcomes as a function of delay.

Reward and reversal learning (inability to reproduce behaviours that lead to positive outcomes and to extinguish behaviours that lead to negative outcomes) [35,36] are elementary cognitive processes of impulsivity [37]. Different experimental paradigms have been used to explore reward and reversal learning, for example the probabilistic reversal learning task proposed by O'Doherty [38], or the probabilistic selection task, proposed by Frank [36]. Behavioural and cognitive studies have identified two main neural systems that are involved in reinforcement and reversal learning in HS [39]. On the one hand, the OFC is implicated in the context of uncertain or changing contingencies [23,38]. In particular, the lateral OFC is activated following a punishing outcome, the medial OFC is activated following a rewarding outcome [38]. On the other hand, the basal ganglia and the neuromodulator dopamine are thought to participate in both action selection and reinforcement learning [40–44], as confirmed by Pessiglione and colleagues in a behavioural and neuroimaging investigation. In that study, the authors demonstrated how dopamine might modulate, during instrumental learning, the magnitude of reward prediction error in the striatum [45].

3. Motor impulsivity

As mentioned above, motor impulsivity refers to the tendency to perform previously learned motor responses despite signals to the contrary. It is frequently measured in the laboratory within the framework of paradigms that infer that motor impulsivity can be quantified using a stop-signal reaction time task (SSRT) or a go/no-go task. As such, a premium is placed on

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the speed or accuracy with which we can inhibit an action that has, as a requisite of the task, become habitual. Thus, slow reaction times (to the 'stop-signal') and inaccurate responding indicate higher degrees of motor impulsivity, a trait that has been demonstrated in populations with an arguably poor ability to inhibit actions, for e.g., those with behavioural and chemical addictions [46–48].

In recent years our understanding of the neural control of response inhibition has benefited from a large degree of attention from researchers using neuroimaging techniques. Using the SSRT and go/nogo tasks, research suggests that a distributed cortical and subcortical network controls our ability to inhibit unwanted actions, and that failures of inhibition can be traced back to altered activity within particular nodes. Areas that have been implicated in normally functioning response inhibition include, but aren't limited to, the inferior frontal cortex (IFC), the SMA, the ACC and STN of the basal ganglia.

HS typically show activity within these areas when performing response inhibition tasks [49,50], and the normal variation of ability to inhibit responses correlates with their degree of engagement [49,51]. Thus, in one account of response inhibition stop-signals are processed in the IFC and are sent via a hyper direct pathway to the STN, which is then activated to inhibit activity within basal ganglia-thalamo-cortical loops related to the action to be inhibited [50]. Stop-signal and go/nogo tasks in which the participant simply attempts to inhibit all go-signals that are followed by the stop-signal, are thought to provide a measure of reactive inhibition, where the need to stop is 'spur of the moment'. However, paradigms that employ conditional stop-signals, in which the stop-signal applies only to a selection of go-signals, may measure response inhibition that is more selective in nature [52], as well as being more 'proactive' in the case of tasks that inform the participant whether a stop response may be required for the upcoming trial. The latter tasks seem to engage the striatum [53] more than the former, suggesting that specificity of the action to inhibit combined with preparation to inhibit requires the indirect basal ganglia pathways to select inhibition of particular actions, whilst reactive inhibition tasks can be performed without striatal involvement and induce a more global stop response. As suggested in a recent review [52], proactive and selective inhibitions may be a more ecologically appropriate simulation for the control of real-life motivational urges such as gambling and shopping than the more global inhibition required for reactive inhibition tasks.

4. Impulsivity in Parkinson's disease

To understand impulsivity in Parkinson's has become important in and of itself since recent revelations regarding the development of impulsive behaviours (like pathological gambling) in PD treated with DRT [55]. The proposed pathogenetic mechanisms for the emergence of impulsivity disorders in PD can be broadly separated into three potentially interacting processes: the contribution of the disease itself to the behaviour, whether as a manifestation of a particular disease phenotype or genotype, or as a compensatory mechanism for the underlying disease process, the contribution of premorbid susceptibility to impulsivity, and the potential contribution of therapeutic agents and their potential interaction with either of above [54].

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5. Cognitive impulsivity in Parkinson's disease

The study of the role of the *disease* itself on cognitive impulsivity has shown controversial results, maybe due to the heterogeneity of the PD population. Regarding decision-making, only few studies have compared de-novo drug-naïve PD patients with HS. These revealed no differences in cognitive performance between PD patients and HS [56]. The majority of studies investigated decision-making in non-demented medicated PD patients, showing in some cases poorer IGT performance in PD patients compared to HS [57,58]. In others, similar IGT performance was reported [59,60]. However, they almost all agreed that there is no relationship between IGT performance and demographic and clinical features of the patients [61]. Looking at time processing, the same controversial results have been produced. In fact, some authors [62] did not find timing deficits in PD patients, whilst others suggested that time estimation, i.e. the 'internal clock', is abnormally slow in PD, [63] and that DRT [64] and deep brain stimulation of the subthalamic nucleus (STN DBS) [65] might reverse this condition.

Many authors have tried to evaluate cognitive impulsivity in different subgroups of PD patients. Compared to PD patients without impulse control disorder (ICDs), PD patients with pathological gambling (PG) showed impaired cognitive impulsivity, i.e. poorer performances on the IGT [66], and preference for immediate over future rewards [67]. Neuroimaging studies have underlined the idea of a *susceptibility* to impulsivity. Indeed in the subpopulation of PD patients with PG compared to PD non-gamblers, there is an abnormal activation of cortical [68] and subcortical [69] areas implicated in impulse control during the task. In particular Steeves et al. underlined the role of the striatum in a recent PET study [70]. The authors, using [11C] Raclopride to compare D2 receptor availability during a control and a gambling task in two groups of PD patients being treated with dopamine agonists (DAs), one with and one without PG, found that patients with PG had increased release of dopamine in the ventral striatum during the gambling task. The result may be due to the agonists themselves or depend on a sensitization of circuits [71] that is also seen in chemical addicts in response to their chosen drug of abuse [72,73], confirming the idea that DAs might also interact with an underlying susceptibility. Along similar lines, a more recent H2(15)O PET study showed that DAs increased the activity related to a gambling task in brain areas implicated in impulse control in PD patients without gambling. In contrast gamblers showed a DA-induced reduction of activity. Thus, by disrupting the inhibitory key functions of those brain areas in vulnerable patients with PD, DAs may foster the development of PG [74]. Similarly, PD gamblers recently have been shown to be more risk prone ON medication, compare to non-gamblers PD [75].

Dopaminergic medication could potentially modulate impulsivity itself at multiple levels and several hypotheses have been advanced to explain the phenomenon. Experiments using probabilistic selection and a transitive interference task in PD patients supported the hypothesis for which dopamine neurons encode positive and negative rewards in a phasic mode. In particular Frank et al., revealed how DRT (in this case a combination of Levodopa and DAs) can worsen learning from negative outcomes [35,36]. DAs, in contrast to Levodopa, tonically stimulate the dopamine receptors, and may therefore block a phasic dopamine dip that serves as a crucial component of the learning signal [35,36]. Those data

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were confirmed by an fMRI study, in which DAs, but not Levodopa, likely preventing pauses in dopamine transmission, impair the negative reinforcing effect of losing mediated by the orbitofrontal cortex [76]. An alternative, but not mutually exclusive mechanism of impaired learning induced by DAs was suggested by Voon [77]; using a reinforcement-learning model it was shown that DAs in susceptible individuals with PD provoke a distorted estimation of the gain cue. In particular, they augment the rate of learning from gain outcomes by increasing striatal prediction error activity. Moreover, some data revealed a specific role for dopamine in controlling the relationship between the timing of future rewards and their subjective value [78]. In this view, DRT seems to speed up the pacemaker during decisions [16]. Intriguing preclinical data recently showed that dopamine might have a controversial role in mediating risk-based decision making, with increased activation of D1 and D2 receptors biassing choice toward larger, probabilistic rewards, whereas D3 receptors appear to exert opposing effects on this form of decision making [79]. To our knowledge however no human data have been done to confirm those findings. Finally, some authors, using the IGT, suggested that therapy might have a specific role in ambiguous risk-taking, acting specifically on the ventral limbic loop [16,59]. Conversely, STN-DBS seems to play a major role in the second part of the task [77,78], which is more related to explicit risk-taking. That said, the literature on STN-DBS and cognitive impulsivity is controversial [80]. In fact, if some study revealed a specific effect on the dorsal executive loop [81,82], others revealed that explicit and implicit stimulus reward learning was unchanged ON and OFF stimulations [83]. Those controversies are possibly related to the different clinical features of the studied population, or to the position of the electrode in the STN, as elegantly demonstrated by Rodriguez Oroz [84], or finally to the experimental task. In fact, as Frank and colleagues [36] suggested, the STN seems to be involved, reducing premature responding, particularly when a response is executed between multiple competing others.

6. Motor impulsivity in Parkinson’s disease

The study of motor impulsivity in patients with PD may allow us to understand the effects of dopamine deficiency on our ability to inhibit motor responses. Further, recently developed surgical treatments for PD have allowed us to probe, and alter, an important node within the neural network responsible for response inhibition.

PD patients are found to perform poorly on measures of response inhibition [85], and this ability is altered during experimental manipulation of the network sub serving response inhibition using DBS. DBS of the STN has been shown to improve the motor symptoms of PD [86] and allows us to interrupt activity within the STN in order that we can investigate its function. However DBS has been shown to impair, improve and to make no change to patients’ ability to inhibit responses. [87–91]. Such discrepancies in the literature may be explained by more general improvements on the task due to improved motor control [92], dissociable temporal effects of stimulation that result in increased impulsive responding as well as improvements in the engagement of inhibitory processes [93], or differences in the effect of STN DBS on inhibitory control depending on whether the ventral or dorsal STN is stimulated [94].

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Specific neuroimaging tools have allowed us to visualise the brain as we apply DBS during response inhibition tasks. For example Campbell et al., used H2(15)O PET to measure STN DBS-induced variability in motor response inhibition [90]. They found that STN DBS caused blood flow changes in the ACC that correlated with a change in response inhibition. This suggests that stimulation of the STN may induce changes in the cortical (i.e. ACC) control of response inhibition, and the more it does so in individual patients, the greater the impairment in response inhibition. A later H2(15)O PET measured blood flow during a Go/NoGo and a control (Go) task to study response inhibition deficits associated with STN-DBS [91]. They found that STN DBS impaired response inhibition, measured as a greater number of errors during NoGo trials. The PET results revealed that changes on the task were accompanied by reduced activation in areas such as the left premotor cortex, pre-SMA, dorsal ACC and IFC. These areas are thought to sub-serve retroactive response inhibition in which a stimulus to stop must be processed and acted upon in order that inhibition is successful.

Thus, the work discussed in PD has confirmed the less direct evidence from neuroimaging in healthy controls that response inhibition depends on activity within cortico-basal ganglia loops. It is alteration of function within these connections that may be at the root of ICDs that develop in dopamine agonist treated Parkinson's patients. As mentioned before, PD patients with gambling problems that develop after DAs are less able to learn from negative outcomes, perhaps due to the tonic occupation by DAs of striatal post-synaptic receptors, which may prevent the dips in dopamine transmission that would normally signal negative outcomes. Extrapolating to behavioural measures of response inhibition might imply that stop-signals are more difficult to respond to when patients are on dopamine agonists due to the more dominant go-signal mediated by post-synaptic occupation of dopamine receptors [36]. However, to the author's knowledge, there have been no studies that have measured motor response inhibition whilst PD patients with dopamine agonist induced ICDs are on versus off medication.

As discussed above, activity in the striatum is modulated by stopping during response inhibition tasks [50], and is more active during periods of increased anticipation of stop-signals [53]. This suggests that the striatum may be involved in particular during proactive stopping, in which a person prepares to respond to stop-signals that are expected, which may be more closely related to the control of motivational urges, such as gambling, than reactive stopping [52]. Indeed, Steeves [70] found greater release of dopamine in the striatum during a gambling task in PD patients with DAs induced gambling behaviour than control PD patients also on agonists but without any gambling problems. Whilst this finding likely represents an inappropriate reward response during gambling for those patients, it may also suggest that abnormal striatal dopaminergic function could lead to impairments in proactive inhibition required for adequate control of motivational urges. Clearly however, more research on the role of dopamine during response inhibition tasks is required in order for us to understand the role dopamine may play in impulse control in PD.

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7. Summary

The available evidence so far supports the idea of impulsivity as a complex concept, involving two major processes, motor impulsivity and cognitive impulsivity. On one hand motor impulsivity seems to have a more clear definition, maybe in relation to the efficacy of the paradigm to delineate a specific domain, related to the activity of specific neural network. That said, recent research has shown that proactive and selective inhibition may be a more ecologically appropriate simulation for the control of real-life motivational urges than the more global inhibition required for reactive inhibition tasks. On the other hand, cognitive impulsivity appears more difficult to define and to evaluate in all of its components. This might be in relation to specific experimental paradigms that do not clearly and totally delimit the cognitive impulsivity framework, and also to the lack of studies evaluating cognitive impulsivity in its entirety. For those reasons, future research in the field should be more extensive, beyond the idea of a one-dimensional subject of study, trying to link impulsivity to other cognitive processes. Considering the key role of dopamine in the impulsivity domain, the study of the PD model, the use of DAs acting on different kinds of dopamine receptors, and the study of the modulation of STN function will be very important to better understand the impulsivity concept itself, and to highlight the pathophysiology of those impulse control behaviours that are becoming more and more frequently diagnosed in the movement disorder field.

So far, the principal results have shown that increased impulsivity in PD patients may relate to the disease itself, to a susceptibility factor, and to the effect of PD treatment. These may modulate reward sensitivity by altering the fine balance between limbic/executive networks in favour of the limbic system. The outcomes are goal-oriented behaviours leading to greater risk or long term loss and decision making impairments, altered time processing and delay overestimation, distorted estimation of the gain and increasing striatal prediction error activity.

STN DBS may also be involved in cognitive impulsivity, in relation to the role of the STN in limbic circuitry and to its role in high-conflict decision-making processes and time processing. However, its role in decision-making and feedback based learning is still debated. More evident is the involvement of STN in motor impulsivity, even if its specific function is in part unknown, maybe in relation to the different functional sub-territories of the nucleus. New experimental studies evaluating impulsivity in all its components and exploring the effects of DRT and DBS should be carried out in order to clarify all these issues.

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