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OPINION

The dark side of dopaminergic therapies in Parkinson's disease: shedding light on aberrant salience

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Psychotic subjects and patients with Parkinson's disease (PD) "on" dopaminergic drugs, especially on dopamine agonists, present a hyperdopaminergic state that interferes with learning processing. These clinical populations present with distinct alterations of learning that share an increased potential motivational significance of stimuli: psychotic subjects may attribute salience to neutral stimuli, while medicated PD patients may overvalue rewards. Herein is discussed the speculative hypothesis that the hyperdopaminergic state induced by dopaminergic treatments, especially with dopamine agonists, may also facilitate the attribution of salience to neutral stimuli in PD patients, altering the physiological attribution of salience. Preliminary empirical evidence is in agreement with this speculative hypothesis, which needs further empirical investigation. The clinical implications of this hypothesis are discussed in relation to behavioral addictions, psychosis proneness, and enhanced creativity in medicated PD patients.

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Introduction

Striatal dopaminergic neurotransmission is overactive in drug-naïve psychotic subjects, both at rest and in response to stimulation, with no compensatory modulation.[1] The overactive dopaminergic neurotransmission may interfere with the attribution of salience, altering the potential motivational significance of stimuli: salience represents the ability of a stimulus to grab attention and drive behavior.[2,3] Salience attribution is altered because the mesolimbic hyperdopaminergic state interferes with the basic mechanism of reward prediction error encoding,[4,5] as experimentally demonstrated in studies reporting impaired learning in schizophrenic subjects.[6–8] In the present account, the unexpected "aberrant" assignment of salience to internal and external stimuli may initially induce a perplexing state marked by exaggerated importance of some percepts and thoughts and increased inner awareness. Such psychotic symptoms as delusions may arise from seemingly plausible top–down cognitive explanations that individuals come up with to understand the persistence of these experiences of internal and external stimuli with unexpected and aberrant salience.[2,9]

Striatal dopaminergic neurotransmission is also overactive in patients at the early stages of Parkinson's disease "on" medication with levodopa or dopamine agonists.[10,11] These drugs restore dopaminergic levels in the early-affected dorsolateral frontostriatal loop (linking the dorsal striatum and dorsolateral prefrontal cortex), but they may overdose the preserved orbital frontostriatal loop (linking the ventral striatum with the medial prefrontal cortex).[12,13] The overdosing effect of dopaminergic drugs may be more severe in patients with younger PD onset, considering that dopaminergic function physiologically declines with aging.[14]

Dopaminergic drugs interfere with phasic processing of rewards provided by ventral striatum dopamine neurons, strengthening dopaminergic peaks (associated with unexpected rewards), and preventing dopaminergic dips (associated with failures of expected rewards), as confirmed by impairments in reward learning induced by dopaminergic therapy in the early stages of PD;[15,16] this effect is stronger for the tonic stimulation provided by dopamine agonists in comparison with the phasic stimulation provided by levodopa.[17,18]

The alteration of reward learning (strengthened dopaminergic peaks associated with rewards, prevented dopaminergic dips associated with failures of expected rewards)

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induced especially by dopamine agonists represents the pathophysiological basis[19,20] of behavioral addictions in PD patients.[21] These include dopamine dysregulation syndrome (DDS),[22] which is an addictive pattern of medication intake, particularly of large doses of dopaminergic drugs in excess of that required to control motor symptoms, and such impulse control disorders (ICDs)[23] as pathological gambling, hypersexuality, compulsive eating, punding, hoarding, and compulsive shopping.

Hypothesis

Psychotic subjects and patients in the early stages of PD "on" dopaminergic drugs present with a hyperdopaminergic state that alters reward processing. The alterations described in these clinical populations are not overlapping but share an increased potential motivational significance of stimuli: psychotic subjects attribute salience to neutral stimuli, while medicated PD patients overvalue rewards (and "neglect" punishments).

On the basis of this shared feature in reward processing, it could be hypothesized that the hyperdopaminergic state induced by dopaminergic drugs in PD patients may also facilitate the attribution of salience to neutral stimuli. This hypothesis could be tested investigating salience attribution and clinical features related to its alteration (such as psychosis and psychosis-proneness) in PD patients in comparison with healthy controls.

PD patients with such behavioral addictions as ICDs and DDS present with more overactive striatal dopaminergic activity[24] and more altered reward processing[25] in comparison with PD patients who do not present these neuropsychiatric manifestations; therefore, the prevalence and severity of salience features could be higher in PD patients with behavioral addictions compared to PD patients without them. These speculative hypotheses should not be primarily investigated in the advanced stages of PD, in which such psychotic features as delusions and hallucinations[26] are mainly due to the widespread cortical diffusion of Lewy-body neuropathology.[27,28]

Saliency and related features in Parkinson's disease

Two studies directly assessed salience features in PD patients. A behavioral study[29] assessed newly diagnosed drug-naïve PD patients before and after 12 weeks of dopamine agonist treatment, with a speeded-up reaction time task and with the probe stimulus preceded by conditioned stimuli signaling monetary reward by color or shape. Dopamine agonists increased both adaptive and aberrant salience in PD patients, that is, formation of real and illusory associations between conditioned stimuli and reward, respectively. Unusual feelings and experiences, considered subclinical manifestations of psychotic-like symptoms, were specifically related to irrelevant and illusory stimulus–reward associations (aberrant salience). The authors concluded that dopamine agonists may rapidly increase psychotic-like experiences in PD patients, possibly by facilitating dopaminergic transmission in the ventral striatum, which results in aberrant associations between conditioned stimuli and reward.

Another study[30] psychometrically investigated 50 medicated PD patients, 12 newly diagnosed drug-naïve PD patients, and 15 healthy controls with the Aberrant Salience Inventory.[31] Dopaminergic medication doses significantly correlated with some features of aberrant salience (increased significance, heightened emotionality, and heightened cognition), and some features of salience (impending understanding) were higher in comparison with drug-naïve PD patients.

One paradigm related to salience attribution is latent inhibition,[32] a process that occurs when an organism is exposed to a stimulus that is not followed by a significant consequence: the stimulus subsequently becomes less effective, as compared to a novel stimulus, in the acquisition of a new association.[33] Latent inhibition has been shown to be dysfunctional in psychotic patients,[34] who allocate more attention to irrelevant stimuli in comparison with healthy controls. Dopaminergic drugs may decrease latent inhibition in de-novo PD patients,[35,36] enhancing at the same time perceptual psychotic-like experiences (changes in subjective feelings in thinking, time perception, and mental "highness"). Psychosis proneness has also been reported in cognitively preserved PD patients, especially in the subgroup with ICDs.[37]

Increased frequency of psychotic symptoms has been reported in PD patients with ICDs[38–40] and DDS[41] in comparison to PD patients without them, and one study[42] directly reported a case series of nondemented patients developing concomitantly both delusional jealousy and hypersexuality. Moreover, several studies reported isolated psychosis in cognitively preserved PD patients when exposed to dopamine agonists.[43–46]

Discussion

The empirical findings presented herein are preliminarily in agreement with the speculative hypothesis that dopaminergic treatments adopted to restore motor functions may interfere with the physiological process of salience attribution in patients in the early stages of PD, especially in those with younger disease onset. Moreover, they are also in agreement with the related speculative hypothesis that this interference effect is stronger in PD patients who present such behavioral addictions as ICDs and DDS. The tonic dopaminergic stimulation of dopamine agonists, rather than the phasic stimulation of levodopa, may cause an attribution of

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salience to neutral stimuli. The altered increased motivational significance of stimuli at the basis of behavioral addictions in medicated PD patients probably could include features related not only to overvalue of rewards but also related to aberrant salience attribution. Therefore, behavioral addictions may be considered a nonmotor side effect of dopamine agonists that may emerge in a subclinical "atmosphere" of altered salience, representing a condition of psychosis proneness and a risk factor for the development of comorbid psychotic features. The decreased latent inhibition induced by dopaminergic drugs may also contribute to alteration of this subclinical atmosphere, in which irrelevant stimuli continue to activate the attention of subjects.

This could explain why PD patients with such behavioral addictions as ICDs and DDS may present increased psychotic features compared to PD patients without behavioral addictions and why in some cases dopaminergic treatments, especially dopamine agonists, may induce the concomitant development of ICDs and psychosis.

This subclinical atmosphere of altered salience/psychosis proneness may represent the "dark" side of dopaminergic treatments in early-stage PD patients, especially those with younger onset. In this subgroup, the overdosing effect of dopamine agonists is stronger considering that dopaminergic function physiologically declines with aging.[14] Behavioral addictions, being associated with more overactive striatal dopaminergic activity[24] and more altered reward processing,[25] are probably also associated with more altered salience attribution, that is, psychosis proneness. From this perspective, disease-related characteristics[28] and such individual characteristics as cognitive functioning, premorbid impulsivity, and previous history of addiction, as well as other psychiatric features, may play the role of moderating factors in the clinical expression of an increased motivational significance of stimuli.

Furthermore, the attribution of salience to neutral stimuli, increasing their motivational significance and inducing an atmosphere of altered salience, could be involved in the physiological bases of enhanced creativity detected in early PD patients on dopamine agonists[47] that is not simply due to an increase of impulsivity nor to behavioral addictions,[48] and is associated with such signs of increased psychosis proneness as schizotypal traits.[49] This speculative hypothesis needs empirical investigation.

Conclusions

Reviewed empirical findings only preliminarily support the speculative hypothesis discussed in the present opinion piece. This hypothesis deserves further empirical investigation. Once supported by empirical data, the clinical implication could be that such behavioral addictions as ICDs and DDS should be considered a clinical indicator of a hyperdopaminergic state associated not only with overvalue of rewards (sustaining addictions) but also with altered salience attribution, increasing the risk of psychotic phenomena. Therefore, an accurate neuropsychiatric assessment covering both risks for addiction and psychosis proneness is needed before beginning any dopaminergic treatment, especially for young-onset PD patients.

Disclosures

Michele Poletti hereby declares that he does not have any conflicts of interest to disclose.

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