Parkinson's disease, visual hallucinations and apomorphine; a review of the available evidence

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Abstract

Background

Visual hallucinations (VH) occur in the clinical course of Parkinson's disease (PD) and are predictive for the development of psychosis and PD dementia. The genesis of VH is related to impaired bottom-up and/or top-down visual processing which have been linked to cholinergic dysfunction and mono-amine imbalance. The risk of developing VH with oral dopamine agonists seems to increase with advancing disease while evidence suggests that in contrast apomorphine is well-tolerated. Beneficial effects of apomorphine on VH have also been reported.

Methods

The aim of this study is to review current evidence relating to apomorphine and VH in relation to its mode of action.

Results

There is little evidence on the efficacy of apomorphine on VH suggesting a positive effect due to the action of its piperidine moiety. This moiety is also found in many anti-psychotics, and has binding sites to specific dopaminergic and serotonergic receptors (5-HT_{2A}). The potential anti-hallucinogenic effect might be related to mixed D_1 and D_2–like receptor agonism and serotonin 5-HT_{2A} receptor antagonism.

Conclusion

It is very likely that the genesis of VH in PD is related to multiple deficient mono-aminergic systems. It is possible that the anecdotal evidence suggesting that apomorphine has a relatively low proclivity to induce VH in PD may be due to its capacity to reduce serotonergic activity and simultaneously enhance dopaminergic transmission.

Introduction

Visual hallucinations (VH) occur commonly in Parkinson's disease (PD) with an estimated prevalence of 22-38%, increasing up to more than 60% after long-term follow-up [1,2]. The most significant risk factors in the development of VH include disease duration, motor symptom severity and cognitive impairment. They become increasingly intrusive in many patients and are believed to be predictive for PD dementia [1].

VH have long been considered a side-effect of dopaminergic medication, based on clinical experience and an early open-label trial [3]. However, in spite of several studies no strong link has been identified between the occurrence of VH and the dosage or duration of dopaminergic medication [1,4,5]. Moreover, VH have also been reported in a few drug-naïve PD patients [6–8]. This suggests that VH are not directly caused by dopaminergic overstimulation, but that treatment may act as a precipitating factor. In contrast, evidence from a number of case series and a single open-label prospective trial suggest that apomorphine (potent dopamine agonist) has the potential to alleviate some of the symptoms of VH [9–12].

We examine the current evidence for the underlying pathogenesis of VH in PD, together with the impact of dopamine agonists in general and apomorphine in particular.

Pathogenesis of visual hallucinations in Parkinson's disease

Collerton and colleagues have proposed the perception and attention deficit (PAD) model, suggesting that VH are caused by disruption of either the bottom-up and/or top-down visual processing mechanisms [13]. In bottom-up processing, visual stimuli reaching the primary cortex are coupled to specific content e.g. shape, colour, and motion. For object recognition, information from the primary

visual cortex is further processed in the inferior temporal cortex via the ventral visual stream [14]. The information received in the parietal lobe provides detail of the spatial content of the visual stimulus, referred to as the dorsal stream. In top-down processing, an interpretation of the visual information is generated based on perceptual expectations and prior knowledge. Visual information from the inferior temporal cortex is dealt with in the lateral prefrontal cortex via the uncinate fascicle [15], and via cortico-thalamo-cortical loops [16–18]. The mediodorsal and reticular thalamic nuclei are essential in gating and filtering relevant visual information [19,20].

Impaired bottom-up and top-down visual processing in PD patients with VH is supported by structural and functional imaging [14], and clinico-pathological studies [15]. PD patients with VH were found to have impaired attention and higher cortical visuoperception, due to prefrontal cortex and parieto-occipital cortex dysfunction respectively on functional imaging [16–19], and higher Lewy body density and alpha-synuclein aggregation was found in prefrontal, temporal and visuoperceptive areas in patients with coexistent PD and VH than age matched controls without VH [20–23].

Central to the PAD modelVisual processing and VH have been linked to dysfunctional neurotransmitter systems is the connection between visual processing, VHs and cholinergic dysfunction [13,16]. Although the majority of the pathophysiological evidence for VH involves disruption of the cholinergic system, there is also support for a dysbalance in mono-aminergic neurotransmitter systems, especially related to dopamine and serotonin.

The role of acetylcholine, dopamine and serotonin in the development of visual hallucinations

a) Acetylcholine

Bottom-up and top-down visual pathways are modulated by acetylcholine. Low cholinergic activity following the use of anticholinergic drugs impairs attention [17,18] and visual processing [19], and can sometimes induce delirium with VH, even in individuals without clinical evidence of PD (Han et al., 2001) [20]. In contrast, use of cholinesterase inhibitors improves attention, thalamic function and visual processing in a dose-dependent manner [17,21–23].

The majority of cholinergic projections to the cortex originate from the nucleus basalis of Meynert (NBM), located in the basal forebrain, and from the pedunculopontine nucleus (PPN), projecting to the thalamus. Comparison of PD patients with and without VH has found greater degeneration of these regions in those with VH [24–26]. There is little *in vivo* clinical data of cholinergic activity in PD patients with VH with cortical cholinergic activity reduced in PD patients with dementia (PDD) compared to those without and a greater clinical response to cholinesterase inhibitors in these patients with VH compared to those without hallucinations [27–29]. An ongoing randomized, placebo-controlled, double-blind phase IV study is currently investigating the effect of rivastigmine in PD patients with VH without dementia (NCT01856738).

a)b) Dopamine

The substantia nigra and ventral tegmental area (VTA) are the major source of dopamine in the brain. The substantia nigra primarily projects to the dorsal striatum, whereas the VTA projects to the ventral striatum and to extrastriatal regions, including the prefrontal cortex, mediodorsal nucleus and lateral

geniculate nucleus of the thalamus and occipital cortex [44–49]. These projections target both D_1-like receptors (abundant in the prefrontal cortex) and D_2-like receptors (high density in the striatum)[50,51].

The rich expression of D_1-like receptors in the prefrontal cortex suggests a key role in top-down processes related to attention, a feature supported by a number of animal studies [30,31]. Absence of selective D_1 agonists and antagonists has complicated study of these specific receptors in humans. However, genetic variation in the breakdown of prefrontal dopamine by the catechol-*O*-methyltransferase (COMT) gene has made it possible to compare high-activity (low dopamine) and low-activity (high dopamine) COMT genotypes. Results from both animal and genetic studies suggest an inverted U-shaped relationship between D_1-like receptor activity and prefrontal function (Figure 2), with both low and high dopaminergic activity impairing function of the prefrontal regions, clinically manifesting as reduced working memory and attention [32,33]. In other words, the optimal prefrontal performance is achieved with intermediate dopaminergic activity and whether stimulation or inhibition of D_1-like receptors yields this optimum depends on the baseline dopaminergic activity in the prefrontal cortex. Enhanced dopamine levels are found in early PD patients resulting in impaired prefrontal functioning [34–36] presumably due to frontal compensation [37]. With disease progression, the number of prefrontal D_1-like receptors is reduced and prefrontal functioning deteriorates [36,38–40].

Dopamine may play a role in visual processing. It is well recognized that dopamine deficiency in the occipital cortex, lateral geniculate nucleus and retina impairs lower-order visual functions, such as color discrimination and visual contrast sensitivity, as well as playing a role in higher-order visual functions, such as motion perception, visual acuity, and colour vision [41]. These deficits can be reversed with the administration of levodopa [41], suggesting a compelling link between dopamine and visual perception. Dopamine appears to play a more specific role in retinal function with concentrations sensitive to light

intensity and a circadian rhythm with lower dopamine concentrations at night and higher levels during the day [41]. Therefore, dopamine seems to be essential in mediating light-adaptive mechanisms in retinal function [42,43].

~~Overall, the stimulation of D_1-like and D_2-like receptors by apomorphine may have different effects on top-down processing, dependent upon concentration of the drug and the clinical disease stage (Figure 2). In early PD, where a relative dopaminergic overstimulation in the prefrontal cortex exists, the addition of apomorphine could potentially worsen top-down processing. However, in late PD a relative shortage of dopamine in the prefrontal cortex may be corrected by apomorphine administration. These findings suggest that other mixed D_1-like and D_2-like dopamine agonists, such as pergolide and cabergoline, could exert similar anti-hallucinogenic effects. However, the evidence to date suggest a distinct effect for the ergolines pergolide and cabergoline indicating that the serotonergic antagonistic properties of apomorphine's piperdine moiety makes an additional and significant contribution [66].~~

b)c) Serotonin

Accumulation of alpha-synuclein and Lewy body pathology is also found in serotonergic neurons located in the raphe nucleus [67]. The median, and to a lesser extent, the dorsal raphe nuclei project directly to the prefrontal cortex, occipital cortex and thalamic nuclei, and indirectly via the striatum [68,69], all potentially having a role in visual processing.

The serotonergic receptor 5-HT_{2A} is widely expressed in the neocortex and suggested to play a role in the pathogenesis of VH. Positron emission tomography (PET) studies comparing PD patients with and without VH demonstrated an increased 5-HT_{2A} binding in prefrontal and visual processing areas [44,45].

A potential explanation for these findings being compensatory post-synaptic up-regulation due to pre-synaptic serotonergic neuronal loss. Neurochemical studies using the 5-HT_{2A} receptor agonist, psilocybin, have also demonstrated a dose-dependent reduction in prefrontal functions (e.g. attention and working memory) and in visuo-perceptive functions (e.g. high-level motion perception) as well as inducing VH in healthy volunteers [46–49]. Interestingly functional imaging studies have demonstrated similar activation patterns in healthy volunteers with psilocybin-induced hallucinations as those seen in PD patients with VH with reduced activity in the occipital cortex and visual pathways, as well as increased activation in the prefrontal cortex [50–53]. Subsequent studies have made use to the 5-HT_{2A} receptor antagonist ketanserin, used to block the effects of psilocybin in healthy volunteers [47,48,54]. These findings, together with the successful use of clozapine in the treatment of PD-related VH (due to predominant 5-HT_{2A} receptor antagonist activity) suggests that treatment of these symptoms in patients with VH might benefit from wider therapy with 5-HT_{2A} receptor antagonists [55]. Use of the selective 5-HT_{2A} antagonist pimavanserin has been shown to resolve psychotic behavior in an animal model (6-hydroxydopamine), while in clinical trials use of pimavanserin, previously demonstrated to be well tolerated, has more recently been reported to have a beneficial effect on VH in PD patients [56–58].

Although the majority of the pathophysiological evidence for VH involves disruption to acetylcholine transmission, there is also support for a role of mono-amine neurotransmitters indicating a need for adaption to the PAD model, particularly in relation to the role of dopamine agonists, most notably apomorphine.

Clinical evidence for the risk of development of visual hallucinations with medical therapiesrelated to dopaminomimetics

a) Oral dopamine agonists and rotigotine transdermal patch

Anecdotal clinical experience and a number of clinical trials have suggested that oral dopamine agonists may exacerbate and unmask VH. In a 2010 meta-analysis the use of dopamine agonists including pergolide (RR 4.80, 95% confidence interval (CI): 2.24, 10.29), rotigotine (RR 4.02, 95%CI: 1.23, 13.11), pramipexole (RR 3.36, 95%CI: 2.41, 4.68), ropinirole (RR 2.84, 95%CI: 1.34, 5.99), cabergolide (RR 1.56, 95%CI: 0.47, 5.21) and bromocriptine (RR 1.10, 95%CI: 0.37, 3.26) was associated with a higher relative risk (RR) of VH compared to placebo [59]. However, no adjustment was made for disease duration, age or cognition, all of which are likely to impact on the development of VH. Studies have shown that use of dopamine agonists in patients >70 years of age is associated with an increased risk of developing VH compared to younger patients [5], while a recent meta-analysis demonstrated that the RR of developing VH increased to 5.24 (95%CI: 2.42, 11.35) in advanced PD patients (age of 61-66 years, disease duration of 5.9-8.9 years) using dopamine agonists on top of levodopa treatment [60].

In contrast to the possible increased risk of dopamine agonists infusion of high-dose levodopa failed to precipitate visual hallucinations in non-demented PD patients [61], and low- dose dopaminergic treatment is rarely complicated with the development of visual hallucinations in other disorders, such as hyperprolactinaemia, raising the possibility that cholinergic and/or serotonergic dysfunction is an essential prerequisite for their occurrence.

It is therefore recommended that in the absence of systemic illness, the dose of dopamine agonist should be reduced if VH develop and that they should be prescribed with caution in PD patients with significant cognitive impairment [62].

b) Apomorphine

No worsening of VH has been reported in advanced PD patients receiving apomorphine treatment with long-term follow-up in descriptive studies [63–66] and apomorphine has even been suggested to have a beneficial effect on VH [9,12]. The antipsychotic potential of apomorphine was first reported in patients diagnosed with schizophrenia [67,68]. In a double-blind, placebo-controlled trial 3 mg subcutaneously-administered apomorphine reduced psychotic symptoms in 18 patients with longstanding schizophrenia [68]. This reduction in psychotic symptoms has also been replicated in several open and controlled trials of the management of acute psychosis patients diagnosed with schizophrenia [69].

The beneficial effects of apomorphine in the treatment of neuropsychiatric symptoms (predominantly VH) in patients with PD have been reported in a number of case series [9–11]. Altogether these case series describe long-term follow-up (8-72 months) of 16 PD patients, 12 with reported VH. Eleven described a dramatic reduction in visual symptoms with only mild persistence in the remaining case [9]. Support for these observations has come from a more recent open-label clinical trial, in which treatment with oral dopamine agonists was replaced with apomorphine [12]. PD patients with VH (n=8) demonstrated an improvement in neuropsychiatric symptoms (measured using the Neuropsychiatric Inventory Questionnaire (NPI-Q), evident after only a week of apomorphine treatment and persisting six weeks later. These findings suggest that apomorphine may be prescribed in PD patients with VH provided there is concomitant reduction in the dose of oral dopamine agonists and/or adequate treatment of existing cognitive deficits [12].

In spite of this evidence, the common clinical perception remains that apomorphine has the proclivity like other dopamine agonists to worsen VH in patients with PD [70]. This may be in part due to those

early anecdotal descriptions of worsening neuropsychiatric symptoms and the absence of a randomized controlled trial of the impact of apomorphine on VH [71–73].

Chemical structure and receptor binding profile of apomorphine

The molecular structure of apomorphine is closely related to dopamine (Figure 1), sharing a benzene ring with two hydroxyl groups, but it also contains a piperidine moiety ($(CH_2)_5NH$), which may be crucial for its proposed antipsychotic effect [74]. This piperidine moiety is also incorporated in the chemical structure of many antipsychotic medications, including piperidine phenothiazines, haloperidol, risperdone, bulbocapnine and other aporphines [75,76]. Based on the structural similarities, it has been argued that the antipsychotic potential of apomorphine is due to the specific action of this piperidine moiety in binding to dopaminergic and serotonergic receptors (particularly 5-HT_{2A}-receptors), producing an antagonistic effect [9,12,76–78].

Apomorphine is a strong dopamine agonist possessing high affinity for both D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) receptors [79]. It also possesses antagonist activity at 5-HT_{2A} receptors and agonist activity at norepinephrine receptors, although affinity at both receptors is relatively weak [80,81]. In order to determine the role of the receptor profile of apomorphine, mono-aminergic projections need to be incorporated into the PAD model of VH.

Overall, the stimulation of D_1-like and D_2-like receptors by apomorphine may have different effects on top-down processing, dependent upon concentration of the drug and the clinical disease stage (Figure 2). In early PD, where a relative dopaminergic overstimulation in the prefrontal cortex exists, the addition of apomorphine could potentially worsen top-down processing. However, in late PD a relative

shortage of dopamine in the prefrontal cortex may be corrected by apomorphine administration. These findings suggest that other mixed D_1-like and D_2-like dopamine agonists, such as pergolide and cabergoline, could exert similar anti-hallucinogenic effects. However, the evidence to date suggest a distinct effect for the ergolines pergolide and cabergoline indicating that the serotonergic antagonistic properties of apomorphine's piperdine moiety makes an additional and significant contribution [59].

The role of mono-amines in the development of visual hallucinations

c) Dopamine

The substantia nigra and ventral tegmental area (VTA) are the major source of dopamine in the brain. The substantia nigra primarily projects to the dorsal striatum, whereas the VTA projects to the ventral striatum and to extrastriatal regions, including the prefrontal cortex, mediodorsal nucleus and lateral geniculate nucleus of the thalamus and occipital cortex [66–71]. These projections target both D_1-like receptors (abundant in the prefrontal cortex) and D_2-like receptors (high density in the striatum)[72,73].

The rich expression of D_1-like receptors in the prefrontal cortex suggests a key role in top-down processes related to attention, a feature supported by a number of animal studies [74,75]. Absence of selective D_1 agonists and antagonists has complicated study of these specific receptors in humans. However, genetic variation in the breakdown of prefrontal dopamine by the catechol-*O*-methyltransferase (COMT) gene has made it possible to compare high-activity (low dopamine) and low-activity (high dopamine) COMT genotypes. Results from both animal and genetic studies suggest an inverted U-shaped relationship between D_1-like receptor activity and prefrontal function (Figure 2), with both low and high dopaminergic activity impairing function of the prefrontal regions, clinically

manifesting as reduced working memory and attention [76,77]. In other words, the optimal prefrontal performance is achieved with intermediate dopaminergic activity and whether stimulation or inhibition of D_1-like receptors yields this optimum depends on the baseline dopaminergic activity in the prefrontal cortex. Enhanced dopamine levels are found in early PD patients resulting in impaired prefrontal functioning [78–80] presumably due to frontal compensation [81]. With disease progression, the number of prefrontal D_1-like receptors is reduced and prefrontal functioning deteriorates [80,82–84].

Dopamine may play a role in visual processing. It is well recognized that dopamine deficiency in the occipital cortex, lateral geniculate nucleus and retina impairs lower-order visual functions, such as color discrimination and visual contrast sensitivity, as well as playing a role in higher-order visual functions, such as motion perception, visual acuity, and colour vision [85]. These deficits can be reversed with the administration of levodopa [85], suggesting a compelling link between dopamine and visual perception. Dopamine appears to play a more specific role in retinal function with concentrations sensitive to light intensity and a circadian rhythm with lower dopamine concentrations at night and higher levels during the day [85]. Therefore, dopamine seems to be essential in mediating light-adaptive mechanisms in retinal function [86,87].

Overall, the stimulation of D_1-like and D_2-like receptors by apomorphine may have different effects on top-down processing, dependent upon concentration of the drug and the clinical disease stage (Figure 2). In early PD, where a relative dopaminergic overstimulation in the prefrontal cortex exists, the addition of apomorphine could potentially worsen top-down processing. However, in late PD a relative shortage of dopamine in the prefrontal cortex may be corrected by apomorphine administration. These findings suggest that other mixed D_1-like and D_2-like dopamine agonists, such as pergolide and cabergoline, could exert similar anti-hallucinogenic effects. However, the evidence to date suggest a

distinct effect for the ergolines pergolide and cabergoline indicating that the serotonergic antagonistic properties of apomorphine's piperdine moiety makes an additional and significant contribution [43].

d) Norepinephrine

Norepinephrine is predominantly synthesized in the locus coeruleus. Noradrenergic axons have widespread projections to the thalamus, hippocampus, amygdala, VTA, pontine tegmentum, and prefrontal cortex with norepinephrine itself having highest affinity for alpha-2 adrenergic receptors [88,89].

The effects of norepinephrine on prefrontal functions also follow an inverted U-shaped curve [90]. Modulation of alpha-2 adrenergic receptors in healthy volunteers revealed inconsistent effects on prefrontal functions [91–93]. In contrast, patients with a presumed prefrontal norepinephrine deficiency (i.e. attentional deficit hyperactivity disorder (ADHD) and schizophrenia) were noted to improve with alpha-2 adrenergic stimulation. Clonidine and guanficine (alpha-2 adrenergic receptor agonists), improved attention and working memory in patients diagnosed with ADHD and schizophrenia [94–96]. A single study has examined the effect of norepinephrine on working memory in patients with PD with use of clonidine [97]. Here the effect was greatest in those with advanced PD compared to early symptomatic individuals, supporting this inverted-U relationship between norepinephrine and prefrontal functioning [97].

There is no currently available data of the effect of norepinephrine on visual perception demonstrating an area with need for further investigation.

e) Serotonin

Accumulation of alpha-synuclein and Lewy body pathology is also found in serotonergic neurons located in the raphe nucleus [98]. The median, and to a lesser extent, the dorsal raphe nuclei project directly to the prefrontal cortex, occipital cortex and thalamic nuclei, and indirectly via the striatum [99,100], all potentially having a role in visual processing.

The serotonergic receptor 5-HT_{2A} is widely expressed in the neocortex and suggested to play a role in the pathogenesis of VH. Positron emission tomography (PET) studies comparing PD patients with and without VH demonstrated an increased 5-HT_{2A} binding in prefrontal and visual processing areas [101,102]. A potential explanation for these findings being compensatory post-synaptic up-regulation due to pre-synaptic serotonergic neuronal loss. Neurochemical studies using the 5-HT_{2A} receptor agonist, psilocybin, have also demonstrated a dose-dependent reduction in prefrontal functions (e.g. attention and working memory) and in visuo-perceptive functions (e.g. high-level motion perception) as well as inducing VH in healthy volunteers [103–106]. Interestingly functional imaging studies have demonstrated similar activation patterns in healthy volunteers with psilocybin-induced hallucinations as those seen in PD patients with VH with reduced activity in the occipital cortex and visual pathways, as well as increased activation in the prefrontal cortex [20,107–109]. Subsequent studies have made use to the 5-HT_{2A} receptor antagonist ketanserin, used to block the effects of psilocybin in healthy volunteers [104,105,110]. These findings, together with the successful use of clozapine in the treatment of PD-related VH (due to predominant 5-HT_{2A} receptor antagonist activity) suggests that treatment of these symptoms in patients with VH might benefit from wider therapy with 5-HT_{2A} receptor antagonists [111]. Use of the selective 5-HT_{2A} antagonist pimavanserin has been shown to resolve psychotic behavior in an animal model (6-hydroxydopamine), while in clinical trials use of pimavanserin, previously

demonstrated to be well tolerated, has more recently been reported to have a beneficial effect on VH in PD patients [112–114].

Discussion

Apomorphine appears to increase lower-order visual perception (e.g. contrast sensitivity), while higher-order perceptual functions (e.g. color perception, visual acuity, visual object, and space perception) remain unchanged. A decrease in contrast sensitivity was found after infusion of apomorphine in healthy volunteers [82,83], suggesting that overstimulation of retinal or cortical dopamine receptors may result in reduced lower-order visual perception. The absence of a positive effect on higher-order perceptual functions in PD patients with VH might be related to a dosing- or a ceiling effect. Conflicting results have been reported in the effect of apomorphine on attention, this variability potentially being related to the clinical stage of PD, although distinct outcome measures and lack of adjunctive clinical data (e.g. use and dosing of other medical therapies) may also have contributed [64,65,84,85].

The beneficial effect of apomorphine in the treatment of VH is based on limited available data and lacks prospectively designed randomized controlled trials. However, it does appear that unlike oral dopamine agonists, apomorphine does not exacerbate symptoms in PD patients with pre-existing VH [12,63–65]. An additional benefit of apomorphine might be its modifying effect on amyloid deposition [86].

Based on the PAD model several deficient mono-aminergic systems may induce VH in PD. Therefore, the treatment of VH in PD will very likely require a combination of therapies dependent on the balance of mono-amines. A combination of apomorphine with cholinesterase inhibitors should be considered in

patients who have developed refractory VH on oral dopamine agonist therapy and who cannot withdraw them without substantial deterioration in motor performance.

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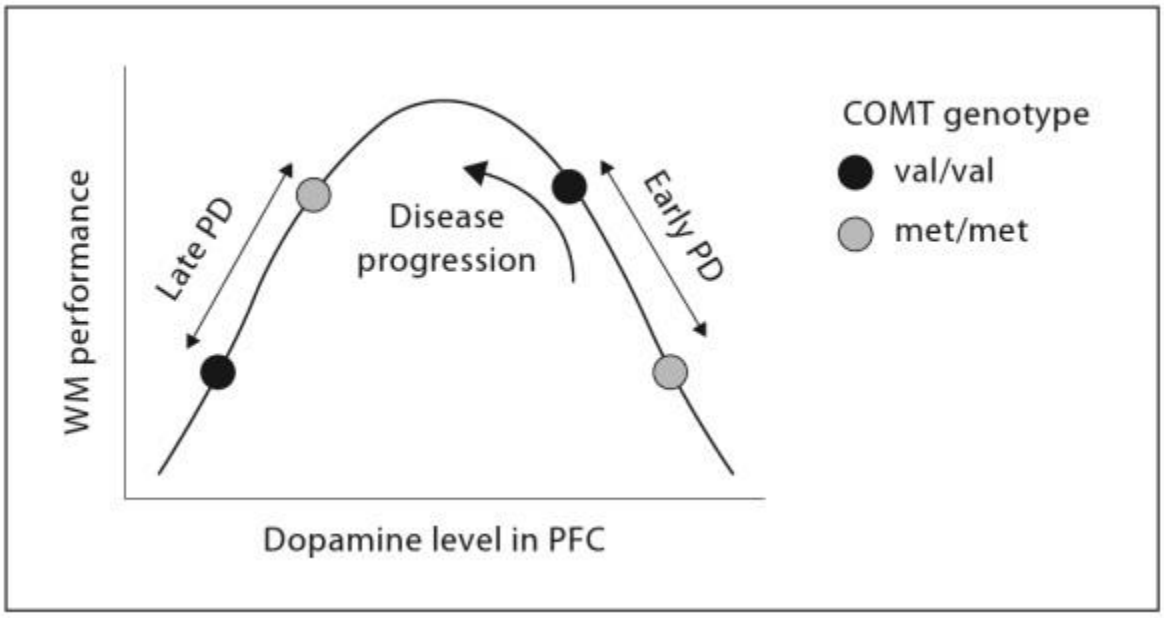
Table 1. Receptor affinity of dopamine agonists. Adapted from Deleu et al. (2004)

	D_1	D_2	5-HT_{2A}	α_2
Aporphines				
Apomorphine	++	+++	-	++
Ergot derivatives				
Bromocriptine	-	+++	++	++
Cabergoline	+	+++	+++	+
Lisuride	-	+++	++	+
Pergolide	+	+++	+++	++
Nonergoline derivatives				
Piribedil	+	+++	0	NA
Pramipexole	0/+	+++	0/+	+
Ropinirole	0	+++	0/+	0
Rotigotine	++	+++	NA	NA

D = dopamine receptor; 5-HT = serotonin receptor; α = α-adrenergic receptor; NA = information not available; - indicates antagonist activity; 0 indicates no affinity; + indicates low affinity; ++ indicates moderate affinity; +++ indicates high affinity.

Figure 1. The chemical structure of dopamine (left) and apomorphine (right). Note the piperidine moiety.

Figure 2 : Relationship between prefrontal functioning and dopamine level in prefrontal cortex



WM : working memory. Val/val: high-activity COMT genotype. Met/met: low-activity COMT genotype. Note that moderate dopamine levels in the prefrontal cortex (PFC) yields optimal prefrontal performance. Adapted from Williams-Gray [36].