

# Explorative Review Of Key Proteins In Impulsive Control Disorders Among Parkinson's Disease Patients

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## ABSTRACT

*As stated by (Weintraub D et al., 2010) 13.6% of those individuals with Parkinson's disease (PD) have one or more forms of impulse control disorders (ICD), whilst the prevalence is greatest in those taking dopamine agonists. Taking a stepwise approach, the current review looks to evaluate the evidence of dopamine 3 receptor's importance to impulsive control disorders amongst those with PD. In conclusion, the literature indicates a central role played by the DRD3 receptor whereby the use of specific DRD3 agonists ultimately led to impulsive control disorders.*

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## INTRODUCTION

Parkinson's disease (PD) is characterised by distinct motor changes, which manifest as shuffling gait and tremors (Jankovic, 2008). The loss of dopaminergic neurons in the substantia nigra pars compacta has been credited with causing these symptomatic effects (Jankovic, 2008). Further to this, behavioural changes have been noted in a sizeable number of PD patients. Termed impulsive control disorders (ICD) in accordance with the World Health Organization disease classification ICD-10, under the F63 code, there are a number of these behavioural conditions. The main ones include: pathological gambling (PG), pyromania, kleptomania and trichotillomania (World Health Organization, 1992).

These impulse control disorders are characterised by impulsivity i.e. behaviour that is repeated continually (Cilia and van Eimeren, 2011). Trichotillomania is a prime example of this, where individuals will continue to pull out their hair.

Until recently the basis of the association between PD and ICD remained largely unknown. All that was understood was that ICD occurred

more in those with PD than when compared to the general population (Cilia and van Eimeren, 2011, Smith et al., 2016). However, Weintraub D et al., (2010) through the use of a cross-sectional study, were able to reinforce this view of an association between PD and ICD, whilst addressing aspects of ICD prevalence among a relatively large cohort of 3090 patients (Weintraub D et al., 2010). Via the use of interviews, patients with PD were assessed according to set criteria whereby subsequent findings found that ICD was prevalent among 13.6% of PD patients. Further to this, (Weintraub D et al., 2010) noted differences in the types of ICDs by gender. Women were more likely to "binge eat" and compulsively buy whilst men were more likely to have compulsive sexual behaviour, however overall the authors suggested a similar prevalence of ICD's between genders. Additionally, their findings also suggested that up to a quarter of those PD patients classified as having an ICD had more than two ICDs. For instance a PD patient who had a pathological gambling ICD may also have a binge eating ICD.

## THE EMERGENCE OF DRD3

There has been interest in the possible association between dopamine agonists and the development

of ICDs within PD patients. In an attempt to investigate this, Mamikonyan et al., (2008) monitored ICDs in PD patients over a period of time. This proved useful in qualifying the involvement of dopamine agonists in ICD development. Mamikonyan and colleagues used Parkinson's patients who already had ICDs, whereby there were 15 in total. Occurring over an average period of under two and a half years (29 months) Mamikonyan et al., (2008) gave the patients questionnaires, such as the Minnesota Impulse Disorder Interview (MIDI), and semi-structured interviews during the follow up period. The most interesting finding was that 80% of patients had their dopamine treatment significantly altered i.e. dopamine agonist treatment by physicians. Within this proportion, dopamine treatment was either ceased completely or reduced considerably. The subsequent effects were reported in ICD diagnoses within the patients. Of the 12 patients who had their dopamine agonist treatment removed or reduced, (three patients remained on same dopamine agonist dose), 10 no longer had ICDs anymore. Although it suggests that across 29 months, removal of dopamine agonists such as Pramipexole and Ropinirole either stopped ICDs or significantly reduced them, the study could be producing manufactured outcomes. For instance, the duration of the dopamine agonist treatment before the study began was not noted. Therefore a certain number of these patients may have been on Pramipexole treatment for 2 years prior to the longitudinal study. Therefore, when that patient's Pramipexole dose was reduced or even removed, it may have had a different effect on ICDs when compared with a patient who had been taking Pramipexole for a month. Additionally, the identification of these patients as having ICDs may not have been uniform or even fair. Semi structured and telephone interviews reinforce this point, whereby each patient's responses may lead to follow up and diverging questions, all of which do not highlight a fair assessment of ICDs. This leads to one conclusion that Mamikonyan et al., (2008) could have strategically used telephone interviews in the second stage of the study to highlight all patients either had partial or full remission of ICD.

Despite the faults with Mamikonyan and colleagues study, Sohtaoğlu et al., (2010) found similar results. In an increased sample the authors analysed 22 Parkinson's patients with ICDs. Further to this, a longer follow up time on average 43.2 months was used. Just as Mamikonyan et al.,

(2008) used two points at which the ICDs were assessed, Time 1 and Time 2 changes to ICDs could be noted in accordance to drug doses. That said the authors altered the medication focus from dopamine agonists to levodopa, between Time 1 to Time 2. So by increasing the levodopa dose and decreasing the dopamine agonist dose at Time 2, 16 patients no longer had ICDs. However the 6 remaining Parkinson's patients that still had ICDs had a significantly different initial dose. With a p value of 0.01, ICD remaining patients had a dose of 5.26mg/day at Time 1 when compared to those patients that recovered from ICDs whose dose was 3.09mg/day at Time 1. Taken together this suggests that the dose was fundamental in recovering from ICDs. Therefore data from the Sohtaoğlu et al., (2010) study did support Mamikonyan and colleagues in suggesting decreasing dopamine agonists decreases ICDs. However Sohtaoğlu et al., (2010) do note that 14 patients were also taking antipsychotic medications, whilst 13 were also taking antidepressants. Therefore, the notion that decreased dopamine agonists reduces or removes ICDs could have been hugely affected by the use of these additional medications. Therefore, a further longitudinal study is required in patients who are not taking any other medications that could interfere with their behaviour. It would ultimately explore the correlation between dopamine agonist treatment and ICD depletion.

Following these previous longitudinal studies, Siri et al., (2015) also conducted longitudinal research in PD patients. This study differed in that they compared both Parkinson's patients, 40 with and 40 without ICDs. PD patients without ICDs were the controls. Further to this, as an extension to the previous longitudinal studies, Siri et al., (2015) performed psychiatric and cognitive tests. The authors wanted to test the possible link between loss of control within cortical regions manifested as cognitive decline and ICD development. However their results indicated no such association, i.e. those PD patients with ICDs did not experience a decline in cognition according to the results of certain cognitive assessments such as Mini-Mental State examination. Further to this within the 40 patients who had ICDs, 16 went into full remission whilst 24 were non-remitters. In comparison to the previous longitudinal studies (Mamikonyan et al., 2008; Sohtaoğlu et al., 2010), that showed relatively high remission rates, Siri and colleagues only found a 40% remission rate. They note a stricter criteria implemented to identify ICD

patients, however this was mainly subjective. The initial assessment was a formal questionnaire based method, which was supplemented with clinical judgements by those with “clinical experience”. It could be argued that their technique is biased against ICD formation in PD patients given this ability to reject those they feel lie outside their ideal of ICDs.

Following the longitudinal studies Dodd M et al., (2005) reinforced previous findings, which indicated a healthy association between dopamine agonists and ICD formation. For instance Dodd and colleagues used 11 PD patients, 9 of which were taking Pramipexole in addition to their levodopa medication. The other two patients were taking ropinirole. To note is the fact that both of these dopamine agonists are highly selective for the D3 receptor. Out of the 11 PD patients, upon initiation of the dopamine agonist, all went on to develop pathological gambling (Dodd M et al., 2005). Subsequently the authors highlighted that it was the dopamine agonists which were responsible for this, as the pathological gambling ceased in 5 patients within 1 month, 1 patient in up to 3 months, another patient in up to 6 months and even when 1 patient who stopped taking the dopamine agonist Pramipexole, the pathological gambling ceased within 48 hours. That said, of the 11 patients who participated, only 4 had never gambled prior to taking the dopamine agonist (1 was unknown). In other words, 6 patients had gambled before and therefore would be more likely to gamble in future. If this sample reflected 11 individuals who had never gambled before, and after dopamine agonist use led to ICD formation (Dodd M et al., 2005), that would have directly highlighted that dopamine agonists were responsible for ICD development. Further to this, 6 of the 11 patients were presented as taking “other psychoactive medications”. This could have interacted with the dopamine agonists positively affecting ICD formation, given that these psychoactive medications are used for behavioural symptoms. Despite this, upon initiation of dopamine agonist treatment, pathological gambling was not the only ICD that the patients developed. In fact hypersexuality, compulsive buying and over eating was present in 5 of the patients. This suggested that the dopamine agonists did not just lead to pathological gambling but the development of ICDs as a whole.

## D3 RECEPTOR LOCALISATION

The localisation of D3 receptors was appropriate to ascertain, given it provides a greater understanding as to the regions of the brain where they are causing effects.

Murray et al., (1994) worked to analyse D2 and D3 localisation within the brain. Via the use of [123I]epidepride in 24 post mortem brains, the authors noted regions of specifically D3 localisation. A negative of the paper was that it stated prior to the production of results that they were only analysing the D3 localisation within the striatum. Murray et al., (1994) were able to analyse binding kinetics, although they found that the Kd did not fluctuate between regions. Further to this, the authors used 7-OH-DPAT in differentiating between D3 and D2 receptors. Given it is around 1000 fold more selective for D3, its ability to displace [123I]epidepride was measured to highlight that D3 receptors were present within that region. The study concluded that the ventral putamen and nucleus accumbens (regions that form part of the ventral striatum) were high in D3 receptors, i.e. they presented increased proportionate binding of D3 receptors within those regions. Further to this, the amygdala, ventral tegmental area (region with the nucleus accumbens forming part of the reward pathway), islands of Calleja, ventral pallidum and globus pallidus were noted as having D3 receptors. On the contrary the dorsal striatum was shown to have little or no D3 binding and thus the authors conclude that the D3 receptors there are insignificant as compared to the other regions noted.

In another study Sokoloff et al., (1990) via the use of molecular cloning in rat brains, the D3 receptor was shown to be different to D1 and D2. Where D1 and D2 are present in the chief dopaminergic areas, the D3 receptors are highly present in the limbic regions. Further to this Landwehrmeyer et al., (1993) who investigated 18 human brain slices were able to show, through use of the radiotracer [125I]iodosulpride, that the rat D3 localisation was comparable to human D3 localisation. The regions that were noted to have D3 expression were the islands of Calleja, nucleus accumbens, caudate and putamen (Landwehrmeyer et al., 1993; Shafer and Levant, 1998).

Thus the expression of D3 receptor is diversely spread throughout the limbic regions. Thus in the methodology, use of the brain atlas will enable further analysis of D3 localisation.

## IDENTIFYING DOPAMINE 3 RECEPTOR EXPRESSION

Determining DRD3 expression could shed light onto its role in Parkinson's disease. That said, a number of studies have looked to analyse D3 receptor expression. For instance, by using human brain slices of specific regions of interest, the putamen, caudate nucleus and nucleus accumbens Hurley et al., (1996) highlighted the regions of D3 receptor expression. The subsequent radioactive labelling with [3H] (+) 7-hydroxy-N,N-di-N-propyl-2-aminotetralin ([3H]7-OH-DPAT) meant that D3 receptors and mRNA were able to be visualised. The author's findings suggested that D3 receptor expression is not altered between Parkinson's disease and healthy control patients. On the contrary, there are a number of studies that have found a decrease in D3 receptor expression in Parkinson's disease patients. In a similar study to Hurley et al., (1996), Ryoo et al., (1998) used autoradiography whereby [125I] trans-7-OH-PIPAT bound to D3 receptors. The resultant findings noted decreases in D3 receptor levels in the putamen, caudate nucleus, internal and external regions of the globus pallidus and also the ventral striatum. Despite this only the external and internal regions of the globus pallidus were not statistically significant. The results suggested that the caudate nucleus and putamen were statistically different with a P value of 0.05 whilst the ventral striatum D3 receptor levels were markedly altered between PD patients and healthy controls. A P value of 0.0005 for the ventral striatum highlights a statistical difference (i.e. a decrease) in D3 receptor within this region. Reinforcing this view, Nagai et al., (1996) noted changes in D3 receptor mRNA from peripheral blood lymphocytes. The result of which was decreased D3 expression among Parkinson's patients compared to healthy controls.

Further to Ryoo and colleagues study, which highlighted a decrease in D3 receptors in Parkinson's disease patients, Morissette et al., (1998) used an animal model of Parkinson's and presented similar results. While only a small number were kept as controls, (3 in total), 9 monkeys were used as Parkinson's like patients. The neurotoxin 1-methyl- 4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) administered to the 9 monkeys was then used to establish the changes in D3 receptors. Like Ryoo et al., (1998) 3H-DPAT was used in the specific binding for dopamine 3 receptors. So this ligand was added to the slices,

which ultimately emphasised regions of binding between the ligand and receptor. The subsequent findings, which were consistent with Ryoo et al., (1998), showed that the D3 receptors were decreased in the MPTP monkeys. However, although this result did suggest similar findings, it was undertaken in an animal and therefore disease progression would be different from humans to animals. Furthermore MPTP use does in part reflect Parkinson's disease however there are differences to the actual human condition. For instance, in the human condition there is the presence of lewy bodies, whereas these are not present in the MPTP form (Jankovic, 2008). Therefore, the resulting decrease in D3 receptors within the MPTP model may not mean that D3 receptors decrease in Parkinson's disease patients. Although there has been research suggesting a change in D3 receptor levels, i.e. a reduction, as found by Ryoo et al., (1998); the results taken from human brain slices. The application of these radioactive ligands to brain slices is therefore not a good indicator of receptor alteration in the presence of Parkinson's disease. As Cho et al., (2007) noted, *in vitro* brain slices are useful in that they enable *in vivo* style measure of neurotransmitters to be conducted. The authors suggest that slices of certain sizes can "retain" brain architecture. This can therefore be probed and subsequently assessed. However it cannot be a full representation of the *in vivo* model of the brain. For instance, mapping or measuring a certain neurotransmitter will be altered from the *in vivo* condition to *in vitro*. There will be a level of depletion, which would mean that the brain slice model would not accurately reflect dopamine levels. That said, new studies are now being used which use Positron Emission Tomography (PET) to present the expression of certain binding within the brain, *in vivo*. This enables the binding of dopamine to specific receptors to be assessed without the depletion that would have resulted from brain slices. Boileau et al., (2009) analysed the alterations in the D3 and D2 receptors. Moreover they also presented findings highlighting the specific changes in the receptor expression within the regions of interest. However recent PET study research have used radioactive ligands, which have not been specific for the D3 receptor. For instance Steeves et al., (2009) used [11C] raclopride to assess the alterations in the D2/D3 dopamine receptors. They analysed the changes in these receptors in regions of interest where one of these was the ventral striatum. They noted a significant decrease in D3 receptors in the



ventral striatum whilst using [11C] raclopride. However as previously mentioned, it is not specific to D3 receptors but rather to both D2 and D3 receptors. Therefore Steeves and colleagues may actually be evaluating the decrease in both D2 and D3 receptors within the ventral striatum. Boileu et al., (2009) however provides an investigation of the D2 and D3 receptors whereby two different radioligands are used. The use of [11C] raclopride and [11C]-(+)-PHNO highlighted changes in striatal regions along with the pallidum. The specific regions of interest evaluated, the globus pallidus, ventral striatum, dorsal putamen and dorsal caudate. The [11C] raclopride did not show any changes in the globus pallidus, dorsal caudate or the ventral striatum. However, there was a significant difference in the dorsal putamen. Furthermore [11C]-(+)-PHNO use showed that there is a decrease in D3 receptor binding in the ventral striatum however it is not significant with 11% decrease. Dorsal putamen D3 receptor binding increased whilst globus pallidus D3 receptor binding decreased. Overall Boileau et al., (2009) claim that the decreased binding of the radioligands [11C] raclopride and [11C]-(+)-PHNO reflects a decreased number of dopamine receptors, namely decreased D3 receptors within that region of interest. Although there are conflicting findings regarding D3 receptor expression, it seems apparent that alterations in receptor expression can in effect contribute to Parkinson's disease aetiology.

## DOPAMINE TRANSPORTER LEVELS

Wu et al., (2015) indicated that although single ICDs have been investigated to a certain degree, multiple ICDs remain untouched. The authors wanted to investigate the levels of striatal dopamine in patients with single ICDs, which could then be compared with those with multiple ICDs and also PD patients without ICDs. A radioligand that is reversibly selective for D2 and D3 receptors, raclopride was used in accordance with a PET scan enabling analysis of dopamine transmission. Using a total of 26 patients, of which 9 were non-ICD controls, 7 had single ICDs whilst 10 had multiple ICDs. Wu et al., (2015) in a similar way to previous studies ensured these individuals were of a similar age, and their age of onset was also close. Focusing further on the use of raclopride, as stated previously it binds in a reversible manner to both D2 and D3 receptors. That said it is receptive to competition from endogenous dopamine, in other

words the author's interpretation suggests that there is a trade off between the radioligand and endogenous dopamine. For instance if there is a greater level of raclopride, it can be construed as having less endogenous dopamine around. However, low levels or a decrease in raclopride would suggest that endogenous dopamine has effectively increased. The authors subsequently analysed raclopride binding in a number of regions of interest on the premise that they would have a better understanding endogenous dopamine levels. These regions included ventral striatum, right and left caudate and the putamen. The subsequent findings indicated no significant differences in 2 of the 3 regions. Put another way, there seemed to be no change in raclopride binding between the three groups, those without ICDs, with single ICDs and those with multiple ICDs. Despite this, a significant difference in raclopride binding was noted in the ventral striatum, which the authors translated as inferring there was an increased level of dopamine transmission within this region. There was a 10.77 percentage decrease in raclopride binding from multiple ICD PD patients in comparison to non-ICD PD patients. The percentage decrease differences between non-ICD controls with single ICD and non-ICD controls and multiple ICDs were statistically significant with the authors highlighting P- values of 0.05 and 0.028 respectively. However, there was no statistical significance between single ICDs and multiple ICDs with a P-value of 0.920, which the authors highlight as part of their analysis as meaning dopamine release is not a differentiating factor between single and multiple ICDs, i.e. it is not related to multiple ICDs occurring at once.

In a similar study to Wu et al., (2015), Callesen et al., (2013) used radioligands to assess dopamine release although only one patient was assessed. Despite the lack of patients Callesen et al., (2013) noted comparable results in that there was a reduction in the radioligand raclopride binding in the ventral striatum. The patient completed a gambling task and the authors subsequently noted that decreased raclopride binding in the ventral striatum signifies a dopamine release upon gambling. Further to Wu and colleagues findings, Steeves et al., (2009) looked to investigate striatal dopamine release in a specific ICD: pathological gambling. Steeves and colleagues highlighted in a PET study, that there were larger decreases in raclopride binding in ventral striatal regions in response to a gambling task. Thus, they concluded that lower raclopride

binding was indicative of increased dopamine release within the ventral striatum.

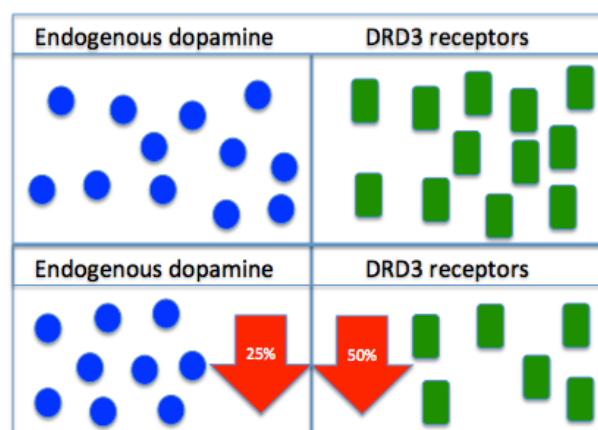
Contrary to these findings of dopamine release, Voon et al., (2014) suggested that dopamine transporter (DAT) changes may be accountable for the “apparent” endogenous dopamine increases in the ventral striatum. In their research 30 PD patients were used comprising of 15 with ICDs and 15 without. Similar to Wu et al., (2015), radioligands were used, although this study used [123I]FP-CIT in accordance with a SPECT scan as opposed to a PET scan. The authors note that [123I]FP-CIT binding correlates with DAT levels. Therefore higher [123I]FP-CIT binding, is indicative of increased DAT levels, this also holds true for lower binding of [123I]FP-CIT binding which suggests lower DAT levels. The study results highlighted that PD with ICDs had lower [123I]FP-CIT binding and therefore lower DAT levels. Also the biggest change came in the right striatum between PD patients without ICDs and PD patients with ICDs, which was statistically significant with a P-value of 0.02. What the author’s note in their analysis is the fact that lower DAT levels means less endogenous dopamine is subsequently viable to be taken up. Therefore, there is more endogenous dopamine in the synaptic cleft and the reduced dopamine clearance can be viewed in some respects as increased dopamine transmission. The failure of DAT to remove dopamine from synaptic clefts could be hypothesised to be causing over stimulation or hyperactivity of the dopamine 3 receptors and thus producing undesired effects such as ICDs.

Referring back to Steeves et al., (2009) and Wu et al., (2015) who suggested that there was an increased dopamine release in the ventral striatum. These studies appear to have constructed a fragmented argument linking dopamine release with ICDs. However as previously discussed, levels of D3 receptor are not evaluated within these studies and also as Voon et al., (2014) note, DAT levels have not been evaluated. Therefore, the claim that dopamine levels have increased in regions such as the ventral striatum without evaluating other factors, such as number of D3 receptors and DAT levels, is misleading. There is a possibility as Morissette et al., (1998) and Ryoo et al., (1998) have shown, D3 receptors may have been reduced. Furthermore endogenous dopamine may also decrease. If the D3 receptor levels decrease to a greater extent than the endogenous dopamine levels, i.e. more endogenous dopamine is present than D3 receptors, it would mean that

the endogenous dopamine within that area readily binds to the receptors available. Therefore, it would give the impression that there is an increased dopamine release within this area, whereas a decreased D3 receptor number may account for this.

As figure 1.1 demonstrates, even a 25% decrease in endogenous dopamine can appear as a release or increased dopamine in that area if DRD3 receptors are reduced further. Taking the example of 12 endogenous dopamine ligands and 12 DRD3; if a 25% decrease occurs with endogenous dopamine, there will be 9 ligands of dopamine left. Also if DRD3 is decreased by 50%, there will be 6 receptors left. Therefore the 9 dopamine ligands will be able to bind more readily or appear as though there is an increase in dopamine, where in fact there is a decrease in dopamine.

Furthermore (figure 1.1) can also be used to explain the change in DAT levels. Voon and colleagues demonstrated that PD+ICD patients had decreased DAT levels. This indicated that less dopamine was being removed from synaptic clefts and thus could appear as though there has just been a release of dopamine. Therefore lower DAT levels in conjunction with hugely decreased DRD3 receptor numbers could result in the appearance of increased dopamine.



(Figure 1.1 represents a theory based on concept of endogenous dopamine increase, incorporating information from Voon et al., 2014 and Wu et al., (2015). The overall result here is that even by a reduction of receptors and endogenous dopamine, it appears as though there is an increased dopamine level).

### BDNF AND D3 RECEPTOR

Brain-derived neurotrophic factor (BDNF) acts in a variety of ways in supporting normal growth of

neurons and has been associated with D3 levels (Guillin et al., 2001). On the basis that BDNF is present in neurons within the VTA (ventral tegmental area), the authors looked to explore the possibility that D3 receptor was influenced or even controlled by BDNF. To do so, BDNF expression was altered and subsequent D3 receptor expression was monitored. In normal wild-type BDNF mice Guillin et al., (2001) showed that D3 receptor expression increased in specific periods of time postnatally within the shell of the nucleus accumbens. This was contrasted to the BDNF knockout, which presented distinctly reduced D3 receptor levels within these same time periods postnatally. As an initial thought, it could be argued that BDNF is important for normal D3 receptor expression. Further to this, Guillin et al., (2001) were able to indicate, with the use of a BDNF gene mutation, that BDNF does not have a role in early development of dopamine neurons. Tyrosine hydroxylase is an enzyme involved in the production of catecholamines, namely dopamine (Daubner et al., 2011). The subsequent BDNF gene mutation did not deplete the mRNA levels of tyrosine hydroxylase. Taken together with the previous findings that BDNF null mice led to reduced D3 receptor expression and that tyrosine hydroxylase mRNA levels are not altered, suggests it can infer that BDNF acts precisely on D3 receptors. In other words BDNF expression serves to effect only D3 receptors, which was further supported when D2 and D1 mRNA levels were recorded within the nucleus accumbens in BDNF null mice which were not affected (Guillin et al., 2003).

Further exploring the possibility that BDNF controls D3 expression, through the use of the radioligand [125I]7-OH-PIPAT Guillin et al., (2003) noted that BDNF and D3 expression are low following birth, whilst they rise correspondingly. In other words, as BDNF rises after birth, so does D3 receptor expression. Supplementing the hypothesis that BDNF controls or at least has some role in D3 expression levels, the authors were able to perform a rescue experiment. Using a neurotoxin 6-hydroxydopamine (6-OHDA) in mice, BDNF was added in an attempt to determine whether D3 expression levels were altered. Surprisingly BDNF administration led to a reversal of decreased D3 expression that subsequent 6-OHDA use had caused. Therefore Guillin et al., (2001) were able to infer that BDNF can act, even

in the loss of dopaminergic neurons, and can offset its effects on D3 receptors.

In a final point regarding BDNF and D3 receptors, Jeanblanc et al., (2006) build upon findings by McGough et al., (2004) who show ethanol consumption is associated with increased BDNF activation. Thus Jeanblanc et al., (2006) subsequently looked to determine if ethanol consumption affected the downstream effectors, namely the D3 receptor. Within striatal brain slices, the authors demonstrated that ethanol consumption does indeed alter downstream effectors by increasing D3 expression only upon incubation with ethanol of greater than 3 hours. This relates to Le Foll et al., (2005) who suggested that just a single cocaine exposure in rats led to increased BDNF levels and that D3 receptor expression remained increased for a longer period of time in the nucleus accumbens. Although this is directed towards addictive behaviour, as opposed to impulse control, there is a clear sense of behavioural modification that is manifested by changes in D3 receptors, which is previously discussed in the literature and my hypotheses suggest this is the basis of ICD development.

## SEROTONIN AND DOPAMINE

Coccaro, (1989) indicates that serotonin is associated with aggression. Further supporting this claim Vermeire et al., (2011) used three groups of dogs, a control, anxious behaviour and an impulsive aggressive behaviour group. Through SPECT and radioligand [123I]-R91150, which is discriminatory for serotonin 2A receptors, the 22 dogs in each group were evaluated to determine whether there was a discernible difference. In other words the study was aimed to see whether these behaviourally different groups had altered serotonin binding. The result demonstrated a highly significant difference (p- value of 0.0056) between the three dog groups, with an overall amplified receptor binding in the impulsive aggressive dogs. However, conducted in dogs, it is likely that defining the criteria for impulsive aggression may be different in humans and thus may produce differing results in humans. Despite this, a study demonstrating the use of fluoxetine (selective serotonin reuptake inhibitor) over placebo in 40 patients showed a significant decrease in irritability and aggression (Coccaro EF and Kavoussi RJ, 1997). Given fluoxetine's role in making sure serotonin takes longer to be up-taken,



and that this drug leads to decreased irritability and aggression, it could be suggested that serotonin has a role in impulsivity, i.e. altered serotonin levels can cause impulsivity. Therefore alongside dopamine receptors and dopamine transporter levels, the overall serotonin levels should be assessed. That said the use of a multi tracer study that analysed the dopamine and serotonin levels suggested that as loss of dopaminergic neurons takes hold i.e. Parkinson's disease, there is a compensatory mechanism in the serotonin system (Ballanger et al., 2016). This increase in serotonin terminals was highlighted through the use of the radiotracer [11C]DASB (Ballanger et al., 2016). The authors report that serotonin must form a compensatory mechanism for lower dopamine levels and claim their multi tracer findings of increased serotonin support this theory. Thus although there is not compelling evidence to suggest a link between dopamine and serotonin levels, studies indicate interplay between the two. The succeeding steps could look at human brain slices for both dopamine and serotonin levels to validate these imaging techniques.

## CONCLUSION

In conclusion, evidence suggests that ICDs are prevalent among PD patients. Moreover the use of dopamine agonists, specifically the D3 selective Pramipexole, at a particular dose led to ICD formation (Dodd M et al., 2005). Subsequently building upon the hypotheses of Cilia and van Eimeren, (2011) and Seeman, (2015) infers the potential for a modified hypothesis whereby the DRD3 protein upon Pramipexole binding had become hypersensitive, thus resulting in over activation of downstream effectors. Therefore, the hypersensitive DRD3 protein would give rise to ICDs such as pathological gambling, overeating and hypersexuality etc. However, further research detailing these downstream effector responses to the Pramipexole binding would be the next logical step in qualifying this hypothesis and thus understanding whether Pramipexole binding to DRD3 alters downstream effectors such as adenylyl cyclase.

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