Investigating Humor Processing in Parkinson's Disease

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Abstract

Dopamine has a demonstrated role in humor processing. Humor comprehension (i.e., “getting the joke”) relies on dorsal striatum (DS) mediated problem-solving mechanisms, whereas humor appreciation (i.e., “funniness”) relies on ventral striatum (VS) mediated reward processing. Despite this, relatively little research has been conducted on potential deficits in humor processing in Parkinson’s disease (PD). The present study investigated the comprehension (i.e., categorization as jokes or non-jokes) and appreciation (i.e., funniness ratings) of verbal jokes and non-jokes in PD patients and healthy age-matched controls while ON and OFF levodopa medication. Relative to controls, PD patients demonstrated reduced humor comprehension in the form of decreased accuracy identifying non-humorous stimuli. Furthermore, controls found jokes to be less funny while ON medication. This suggests that dopamine hypoactivity in the DS of PD patients could contribute to problems understanding humor, whereas levodopa can reduce the rewarding nature of humor via overdose of the VS.

Keywords

Parkinson’s disease; levodopa; humor comprehension; humor appreciation; dopamine; dorsal striatum; ventral striatum
Summary for Lay Audience

Humor is a ubiquitous and unique human cognitive ability, with two fundamental components. The first, humor comprehension, or “getting the joke”, is associated with a part of the brain called the dorsal striatum (DS) that is involved in problem-solving. The second, humor appreciation, refers to subjective amusement experienced in response to funny jokes, and relies on the ventral striatum (VS), an area of the brain responsible for processing pleasurable rewards. The DS and VS are influenced by a neurotransmitter molecule called dopamine. Parkinson’s disease (PD) is a neurodegenerative disease caused by the death of dopamine-producing neurons in the brain, leading to dopamine deficiency in the DS, followed by the VS in later stages of the disease. The frontline treatment for PD is to replace dopamine with a medication called levodopa. However, levodopa can sometimes create an overload of dopamine in the VS, particularly early in the disease, which can cause problems with VS-mediated functions. Surprisingly, humor processing has been relatively understudied in PD, although it is likely that the disease’s dopamine dysfunction can cause problems to DS-mediated humor comprehension, whereas levodopa could cause problems to VS-mediated humor appreciation.

We investigated humor comprehension and appreciation in 10 PD patients and 10 age-matched healthy controls while ON and OFF levodopa. Participants listened to joke and non-joke audio clips and were asked to make judgements about them. The first judgement was to categorize audio clips as jokes or non-jokes. We found that PD patients had more difficulty categorizing non-jokes, which is indicative of a deficit in humor comprehension. The second judgement was to rate how funny each audio clip was. We found that control participants rated jokes as less funny while ON levodopa, suggesting that VS dopamine overdose via levodopa can indeed lead to reduced humor appreciation. However, our patients did not show differences in humor appreciation ON or OFF levodopa, likely due to their relatively later disease stage. Overall, these results suggest that humor comprehension deficits are present in PD, and that treatment with levodopa could cause further problems in the form of reduced humor appreciation for patients early in the disease.
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List of Abbreviations

ACC  anterior cingulate cortex
AMNART American version of the Nelson Adult Reading Test
ANOVA analysis of variance
BAI Beck Anxiety Inventory
BDI-II Beck Depression Inventory II
BIS Barratt Impulsiveness Scale
BL-VAS Bond & Lader Visual Analogue Scale
COMT catechol-o-methyltransferase
dACC dorsal anterior cingulate cortex
DBS deep brain stimulation
dmPFC dorsomedial prefrontal cortex
DS dorsal striatum
EEG electroencephalography
ESS Epworth Sleepiness Scale
fMRI functional magnetic resonance imaging
GABA gamma-aminobutyric acid
GPe globus pallidus external segment
GPi globus pallidus internal segment
IFG inferior frontal gyrus
IPL inferior parietal lobule
IQR interquartile range
ITG inferior temporal gyrus
LED levodopa equivalent dose
L-DOPA l-3,4-dihydroxyphenylalanine (levodopa)
MC motor cortex
MDS Movement Disorder Society
MDS-UPDRS Movement Disorder Society Unified Parkinson’s Disease Rating Scale
MFG middle frontal gyrus
MoCA Montreal Cognitive Assessment
mPRC medial prefrontal cortex
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<th>Abbreviation</th>
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<tr>
<td>MSN</td>
<td>medium spiny neuron</td>
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<td>MTG</td>
<td>middle temporal gyrus</td>
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<tr>
<td>N-FOG</td>
<td>New Freezing of Gait Questionnaire</td>
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<tr>
<td>NAcc</td>
<td>nucleus accumbens</td>
</tr>
<tr>
<td>OFC</td>
<td>orbitofrontal cortex</td>
</tr>
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<td>OHQ</td>
<td>Oxford Happiness Questionnaire</td>
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<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
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<td>PET</td>
<td>positron emission tomography</td>
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<td>PreMC</td>
<td>premotor cortex</td>
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<td>RHD</td>
<td>right hemisphere damage</td>
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<td>RT</td>
<td>response time</td>
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<td>SAS</td>
<td>Starkstein Apathy Scale</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SEM</td>
<td>standard error of the mean</td>
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<tr>
<td>SFG</td>
<td>superior frontal gyrus</td>
</tr>
<tr>
<td>SHQ-6</td>
<td>6-item Sense of Humor Questionnaire</td>
</tr>
<tr>
<td>SMA</td>
<td>supplemental motor area</td>
</tr>
<tr>
<td>SNc</td>
<td>substantia nigra pars compacta</td>
</tr>
<tr>
<td>STG</td>
<td>superior temporal gyrus</td>
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<tr>
<td>STN</td>
<td>subthalamic nucleus</td>
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<tr>
<td>TAS-20</td>
<td>20-item Toronto Alexithymia Scale</td>
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<tr>
<td>TPJ</td>
<td>temporoparietal junction</td>
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<tr>
<td>vmPFC</td>
<td>ventromedial prefrontal cortex</td>
</tr>
<tr>
<td>VS</td>
<td>ventral striatum</td>
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<td>VTA</td>
<td>ventral tegmental area</td>
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Chapter 1

1 Introduction

Humor is arguably one of the most uniquely human cognitive abilities. Although some have proposed that other animals are capable of “laughter” (a panting-like vocalization during social play; Gervais & Wilson, 2005), there is little evidence indicating that other animals are able to tell jokes, laugh at another’s expense, and appreciate unintentionally humorous situations. Evidence suggests that humor has existed for at least 35,000 years (Polimeni & Reiss, 2006b), and that it has evolved to serve adaptive purposes, namely that of facilitating and smoothing interpersonal relationships (Gervais & Wilson, 2005; Polimeni & Reiss, 2006b). Although there are some cultural differences in humor appreciation (e.g., people from Western cultures tend to value humor more highly; Jiang et al., 2019; Yue et al., 2016), no culture has been discovered that does not utilize humor (Fry, 1994; Kruger, 1996). The fact that humor is ubiquitous is widely considered the strongest piece of evidence for the theory that humor evolved through natural selection (Fry, 1994; Kruger, 1996; Polimeni & Reiss, 2006b; Weisfeld, 1993).

1.1 Theories of Humor

1.1.1 Ostracism and Indirect Reciprocity Theory

The greatest adaptive purpose of humor is widely accepted to be its ability to manipulate social encounters, but the ways in which humor can be used interpersonally has been debated by researchers for decades. For example, early humor theorists suggested that humor was primarily used to elevate one’s social status at the expense of another’s. This “ostracism and indirect reciprocity” theory posits that humor is elicited through jokes or tricks that ostracize another individual or group, either by directly putting them down or by leaving them out of an emphasized camaraderie with others (R. D. Alexander, 1986). These mechanisms also work to reinforce the humorist’s elevated social status with others who find the joke amusing. However, this theory is limited in several ways. For example, it does not explain self-deprecating humor in which the joke-
teller is also the victim of the joke. If humor’s main adaptive purpose is to raise one’s own social status, it should not simultaneously lower it. The influence of group norms and social power are also important considerations. Jokes that bring down others are not always received well by the social group, and could negatively impact the social status of the joke-teller (Fine & De Soucey, 2005; Gutiérrez et al., 2018; Knegtmans et al., 2018). There is also the question of whether jokes must always be ostracizing. Alexander (1986) contends that this is impossible. For example, although some puns might contain content that is not directly harmful to any individual or group (e.g., “Do you know what happens when frogs park illegally? They get towed.”), the listener of the pun is inevitably being tricked. Weisfeld (1993) suggests that whether humor necessarily exists at the expense of another is irrelevant; the fact that the joke-teller elicits feelings of amusement in others that reinforces an elevated social status is enough for humor to be adaptive in social situations.

1.1.2 False Alarm Theory

In most cases, telling a joke involves feeding the listener information, which leads them to believe in a certain outcome. The punchline introduces a sudden incongruity that makes the listener question their expectations and reinterpret the original information. Although the ostracism and indirect reciprocity theory focuses on the individual social benefits attained by the joke-teller, Ramachandran’s (1998) “false alarm theory” focuses more on humor’s role in benefitting the social group. He suggests that laughter might have evolved as a mechanism to communicate the detection of a benign incongruity to the rest of the social group. Of course, some situations that have an unexpected twist (i.e., incongruity) might involve potential danger, for example, if a dog suddenly runs into the path of a car driving down a country road. However, sometimes this twist is rendered innocuous, such as if the ‘dog’ turns out to simply be a plastic bag blowing in the wind. Ramachandran (1998) proposes that humor ensues when the sudden twist or incongruity is deemed trivial, and that laughter communicates to the rest of the social group that there is no real threat present. This would allow the group to conserve energy and resources that might otherwise be wasted on investigating potentially dangerous situations. He also suggests that over time, as the need for alerting the social group diminished, humor has
taken on other cognitive and social roles. For example, humor might paradoxically be used in times of distress in order to trivialize an otherwise disturbing situation. This has been well documented following tragic events such as the sinking of the Titanic, assassination of John F. Kennedy, the Challenger explosion, and 9/11 (Chovanec, 2019; Dundes, 1987; Kuipers, 2002, 2005). In fact, evidence suggests that this dark style of coping humor is associated with reduced existential anxiety (Morgan et al., 2019).

1.1.3 Incongruity Resolution Theory

A typical joke follows a standard structure with two key components. The first is the set-up (e.g., “A man asked for a small donation toward the local swimming pool”), which typically provides the listener with contextual information. The second is the punch line (e.g., “I gave him a glass of water”). A joke’s set-up cleverly manipulates the brain’s tendency to make predictions about the world and its development of expectations for what will come next. In the given example, upon hearing the joke’s set-up one would probably expect to hear that the solicitor will be given a small monetary donation. However, the punch line overturns these expectations and produces a sudden incongruity between the brain’s predictions (i.e., that a monetary donation will be given) and the information that has been revealed (i.e., that the “donation” given is in fact a glass of water to fill the pool). This sudden incongruity is touted by many to be humor’s most vital feature (Ramachandran, 1998; Suls, 1972; Wyer & Collins, 1992). Indeed, if the punch line could be predicted (if one had heard the joke previously, for example) then the joke would not be as funny.

However, according to Suls (1972), incongruity is not enough. He further explains that for humor to ensue, an incongruity must be resolved though some cognitive problem-solving mechanism by which we can make sense of the punch line within the context provided by the set-up. In our working example, we must come to understand that a glass of water could indeed be used as a small contribution toward the pool – to the water of the pool, that is. This is the basis for humor comprehension, or “getting the joke”. If the incongruity cannot be resolved, then one cannot comprehend the joke and will simply be confused.
1.1.3.1 Incongruity resolution in puns

Puns are a unique form of verbal joke that contain ambiguous words (i.e., “play on words”) that have double meanings. These can be either homophones, which sound the same but are spelled differently (e.g., *toad* vs. *towed*), or homonyms, which are spelled and sound the same (e.g., *bar* as in a metal pole vs. *bar* as in a drinking establishment). Puns produce incongruity by simultaneously invoking both meanings of an ambiguous word (Bekinschtein et al., 2011). For example, the pun “Why does a chicken coop have two doors? If it had four doors it would be a chicken sedan” utilizes both meanings of the ambiguous word *coop/coupe*. In its set-up, this pun prepares the listener to interpret the word as a poultry house. However, the punch line provides an additional interpretation of the word referring to a sports car. This incongruity is resolved as the listener comes to understand that both meanings of the word are simultaneously valid within the given context. If the listener was unable to retrieve the secondary meaning of the word (i.e., *coupe*), they would be unable to “get” the joke.

Of course, there are situations that invoke incongruity resolution through the use of ambiguous words, but which are not intentionally humorous. For example, the phrase “The other day I went to the bank with my girlfriend,” prepares the listener to interpret the word *bank* as a financial institution. When this is followed up by “We had a really nice time by the water,” the listener experiences an incongruity between the expected and actual meaning of the word *bank*. The listener resolves this incongruity by accessing the subordinate word meaning (i.e., by the river), but humor does not ensue. This is because only one of the word meanings is contextually appropriate.

1.1.4 Reversal Theory

Suls’ (1972) Incongruity Resolution Theory has been met with several criticisms, the largest being that there are many situations in which incongruity resolution occurs but does not elicit humor, such as in our un-funny ambiguity resolution example above. Apter’s (1982) reversal theory puts forth two additional features of humor that extend beyond pure incongruity resolution.
The first is that incongruity resolution must not cause a complete abandonment of one’s original expectation. In the pool donation example joke, the punch line does not invalidate the fact that the solicitor was originally asking for a monetary donation. For our chicken coop/coupe pun, the punch line still follows the original question about the number of doors on the coop. However, in the financial bank/river bank unfunny ambiguity example, we must completely re-interpret our original expectation based on the provided context. The idea of a couple travelling to a financial institution has been completely invalidated and replaced by the notion of a couple sitting by a river.

The second is that the resolution must not lead to some more meaningful discovery, that is, the reinterpretation must reveal a more mundane or unimportant reality. In our pool example, a glass of water is obviously a quite trivial contribution to the solicitor’s campaign. A response of, “Sure! I have a water company and can fill the entire pool for you”, would have still produced incongruity, but would be a more meaningful response and thus not as humorous. This also explains why other forms of incongruity resolution, such as re-evaluating the evidence in a mystery novel upon a sudden plot twist, are not humorous. The new interpretation of the evidence is now much more important in the context provided by the plot twist (Wyer & Collins, 1992).

1.1.5 Comprehension-Elaboration Theory

Wyer and Collins (1992) extend on the previously described theories even further. They propose that in addition to humor comprehension, greater amusement can ensue if we cognitively elaborate on the situation. These elaborations could include imagining the consequences of a humorous situation (e.g., the solicitor’s reaction upon being handed a glass of water), visual imagery of the reinterpretation (e.g., imagining the pool being filled up by small glasses of water), or even evaluating the moral status of the joke-teller (e.g., does this person underestimate the importance of community resources?). Humor elaboration explains why we might still find certain jokes funny upon hearing them for the second time; if further elaborations can be made, the humor can continue to be appreciated. However, jokes with low “elaboration potential” might not evoke amusement upon a second listen.
1.2 Humor Comprehension and Appreciation

The theories described above bring to light an important distinction between two aspects of humor processing: humor comprehension and humor appreciation. Comprehension, or “getting the joke”, involves incongruity detection and resolution through reinterpretation and reappraisal. Humor appreciation describes one’s subjective feelings of amusement or mirth after a joke has been understood, incorporating features such as laughter and Wyer and Collins’ (1992) elaboration process. Importantly, comprehension does not necessitate appreciation. That is, one can “get the joke” but not find it very funny. On the other hand, it is uncommon to experience true humor appreciation without being able to understand a joke. Therefore, it is highly likely that humor comprehension and appreciation are distinct cognitive processes with separable neural bases. Humor comprehension is in many ways a problem-solving process, involving set-shifting, decision making, and in the case of puns, lexical ambiguity resolution. However, humor appreciation produces feelings of pleasure and happiness, and likely invokes the reward network of the brain. Therefore, neurological insults such as neurodegeneration or brain damage could affect humor comprehension and appreciation in different ways, depending on the extent and location of the damage.

1.2.1 Evidence from lesion studies

Support for the distinction between humor comprehension and appreciation comes from an evaluation of the literature surrounding humor processing deficits in patients with brain lesions. For example, a published case study describes a patient who underwent surgical removal of a bilateral frontal groove meningioma with subsequent loss of humor appreciation, despite being able to fully comprehend humor (Patrikelis et al., 2017). Studies investigating patients with right hemisphere damage (RHD) have found that this group demonstrates great difficulty comprehending humor, yet surprisingly has a preserved ability to appreciate humor (Bihrl et al., 1986; Bricker, 1999; Brownell et al., 1983; Chau, 2010; Dagge & Hartje, 1985). This interesting finding has been clarified by interviews with RHD patients who express that they often feel as though humorous stimuli *should* be funny, but they cannot pinpoint the reason why (Bricker, 1999).
1.2.2 Evidence from neuroimaging studies

Several neuroimaging studies have endeavored to investigate the specific brain regions underlying humor comprehension and appreciation. The majority of these studies use very similar paradigms in which participants undergo a functional magnetic resonance imaging (fMRI) scan while they are exposed to humorous and non-humorous stimuli (e.g., cartoons, auditory verbal jokes or puns). Participants are asked to indicate whether they find each stimulus funny or not funny, which is typically used as an indicator of humor comprehension. After the scan, participants provide a “funniness” ratings for the stimuli (usually on a scale with lower numbers indicating less funny and higher numbers indicating more funny), which can then be correlated with brain activity during the scan as an indication of humor appreciation. For example, Bartolo et al. (2006) used this methodology with cartoon stimuli, and found activation of a network involving the right inferior frontal gyrus (IFG), left superior temporal gyrus (STG), left middle temporal gyrus (MTG), and left cerebellum during humor comprehension. They found activation of the same network, with the addition of the left amygdala, when using subjective funniness ratings as independent variables. Similarly, Goel and Dolan (2001) used this paradigm with auditory joke stimuli, and found activation of the bilateral posterior MTG, left posterior inferior temporal gyrus (ITG), and left IFG during humor comprehension. In a conjunction analysis for humor appreciation, they found activation in the ventromedial prefrontal cortex (vmPFC) that covaried with subjective funniness ratings.

However, there are several major flaws to the methodological design used by these prior studies. First, the distinction between humor comprehension and appreciation is not entirely clear, as the dichotomous (funny vs. not funny) and continuous (funniness rating) responses appear to measure quite similar constructs. Furthermore, the dichotomous classification of funny vs. not funny precludes humor comprehension in the absence of humor appreciation. If a participant understands that a stimulus is intended to be a joke (i.e., demonstrating humor comprehension), but does not experience subjective amusement (i.e., humor appreciation), it is not clear whether they should they rate the stimulus as funny, or not funny. It seems as though the distinction between funny and not
funny would be a better approximation of humor appreciation. Indeed, Mobbs et al. (2003) used a nearly identical design, yet operationalized humor appreciation with a dichotomous funny vs. not funny response. They found similar cortical activation to previous studies, including the left temporo-occipital junction, left lateral IFG, supplementary motor area (SMA), and dorsal anterior cingulate cortex (dACC). In addition, they found activation in a subcortical network involving the anterior thalamus, nucleus accumbens (NAcc), ventral tegmental area (VTA), and amygdala, which was taken to indicate that humor appreciation engages the subcortical reward network.

Instead of asking participants to rate stimuli as funny or not funny, Samson et al. (2008) directly asked whether or not they understood the joke. This method provides a much clearer measure of humor comprehension. In their fMRI study, they found that jokes which were understood tended to activate the IFG, temporoparietal junction (TPJ), supramarginal gyrus, and vmPFC. Although Samson et al. (2008) provided a significant improvement over the typical methodology, they also gathered funniness ratings outside of the scanner, which precluded the precise identification of a humor appreciation network. Studies that have include funniness ratings gathered inside of the scanner (e.g., Berger et al., 2018) indeed gain an accurate measure of humor appreciation. However, funniness ratings alone make it impossible to tell whether a stimulus that is rated low in funniness was not appreciated or not comprehended in the first place. Therefore, the simultaneous acquisition of both humor comprehension and humor appreciation measures is essential.

Campbell et al. (2015) recently devised a clever, yet simple, solution to clearly separate humor comprehension and appreciation processes that can be used during neuroimaging. Using a trichotomous response profile, participants could indicate whether they thought a stimulus was 1) a funny joke (FJ), 2) a not funny joke (NFJ), or 3) not a joke at all (NJ). The NFJ response option allows for the demonstration of comprehension without the experience of appreciation. To our knowledge, this is currently the only study that has successfully distinguished humor comprehension and appreciation using this simple method. By contrasting NFJ-NJ trials, significant activation implicating humor comprehension was found in the left IFG, bilateral temporal poles, and bilateral TPJ.
Furthermore, humor appreciation was investigated by contrasting FJ-NJ trials, which demonstrated significant activation in the bilateral substantia nigra and amygdala. Furthermore, a voxel-level FJ-NFJ contrast demonstrated significant activity in the left superior frontal gyrus (SFG).

Despite methodological limitations, it is clear that distinct brain networks exist for humor comprehension and appreciation. Humor comprehension implicates the IFG, medial frontal gyrus (MFG), inferior parietal lobule (IPL), TPJ, MTG, and SFG (Azim et al., 2005; Bartolo et al., 2006; Bekinschtein et al., 2011; Campbell et al., 2015; Chan et al., 2012, 2013; Goel & Dolan, 2001; Martin & Ford, 2018; Mobbs et al., 2003, 2005; Samson et al., 2008; Shibata et al., 2014; Wild et al., 2003). These areas overlap with those involved in problem-solving (Anthony et al., 2018; Becker et al., 2019; Liu et al., 2012), decision-making (Vickery & Jiang, 2009), response inhibition (Hu et al., 2016; Hughes et al., 2013), language processing (Davey et al., 2016; Liakakis et al., 2011), sensory incongruity detection (Papeo et al., 2010), and theory of mind (Biervoye et al., 2016; Devaney, 2018; Igelström & Graziano, 2017; Sellaro et al., 2015; Sowden et al., 2015), all of which are cognitive processes that humor comprehension relies on. On the other hand, humor appreciation engages mesocorticolimbic areas such as the VTA, NAcc, amygdala, hippocampus, and vmPFC (Azim et al., 2005; Campbell et al., 2015; Chan, 2016; Chan et al., 2012; Goel & Dolan, 2001; Martin & Ford, 2018; Mobbs et al., 2003, 2005; Shibata et al., 2014; Wild et al., 2003). These areas have demonstrated roles in reward and motivation, showing increased activity during social reward (Bell et al., 2013; V. G. Weiss et al., 2015), alcohol cues (Filbey et al., 2008), monetary gains (Carlson et al., 2011; Goldstein et al., 2007), and highly palatable foods (Siep et al., 2011; Sinclair et al., 2015).

1.2.3  **Humor processing deficits in autism and schizophrenia**

There also exists a large body of research on humor processing deficits in various neuropsychiatric disorders and diseases. Two of the most commonly studied are autism spectrum disorder and schizophrenia. For example, Wu et al. (2014) found that high school students with autism are worse at comprehending humor compared to students without autism. The same study found that the autistic students had greater appreciation
for nonsense humor compared to classical incongruity resolution-based humor. This supports findings that suggest that autistic individuals have a tendency to choose incoherent, yet humorous, punchlines for joke set-ups instead of coherent humorous endings (Emerich et al., 2003; Ozonoff & Miller, 1996). Samson and Hegenloh (2010) propose that autistic individuals might have difficulties comprehending and appreciating humor due to their difficulties perceiving social cues and utilizing theory of mind, as well as their tendency to focus heavily on the non-humorous details of jokes. Kana and Wadsworth (2012) demonstrated greater activation in the right hippocampus, bilateral IPL, right MFG, and right lingual gyrus in autistic individuals during pun comprehension compared to controls. Overall, the autistic group had more widespread and bilateral activation compared to the control group, which the authors posit is evidence of the use of compensatory mechanisms in retrieving appropriate word meanings.

Schizophrenia patients also have demonstrated reductions in their ability to comprehend (Gomez, 2000; Polimeni & Reiss, 2006a) and appreciate humor (Bozikas et al., 2007). Similar to autistic individuals, patients with schizophrenia are more likely to choose nonsense humorous punchlines for joke set-ups compared to coherent humorous endings (Gomez, 2000). Furthermore, neuroimaging studies have identified hypoactivation in cortical areas relevant to humor processing in schizophrenic patients, relative to controls. For example, schizophrenia patients demonstrate less activity in the right posterior STG, left dorsomedial MFG and SFG, and dACC during the processing of verbal puns (Adamczyk et al., 2017). Another study found that schizophrenic patients had reduced activation in the IPL compared to controls during the processing of visual cartoon jokes (Adamczyk et al., 2018). Berger et al. (2018a) conducted a similar visual cartoon study, finding reduced activation for funny cartoons in schizophrenics compared to controls in the anterior cingulate cortex (ACC), medial prefrontal cortex (mPFC), SFG, MFG, and bilateral insula. Reduced activation was also detected in subcortical regions including the bilateral putamen, right caudate nucleus, and left amygdala. Furthermore, reduced functional connectivity between the mPFC and right caudate nucleus was observed during the processing of funny cartoons for schizophrenic patients compared to controls, which was positively correlated with funniness ratings.
1.2.4 The role of dopamine

The evidence presented so far eludes to the notion that dopamine plays an important role in humor processing. Firstly, dopamine is involved in several cognitive and affective processes that underlie humor comprehension and appreciation, respectively. For example, dopamine appears to be essential in lexical ambiguity resolution, which is particularly important for the processing of verbal puns. In Copland et al. (2003), healthy participants who were given levodopa (a dopamine precursor) demonstrated faster reaction times (i.e., greater priming) to dominant word meanings (e.g., bank as in financial institution) compared to participants who were given a placebo. Similarly, Copland et al. (2009) found slower reaction times to subordinate word meanings (e.g., bank as in river bank) in participants given levodopa compared to those given a placebo. Furthermore, this was associated with reduced activity in the right ACC. This evidence suggests that within semantic networks, elevations in dopamine tend to increase signal strength for more salient word meanings while suppressing less salient ones.

Second, aberrant dopamine neurotransmission has been implicated in both autism spectrum disorder and schizophrenia. Pavâl (2017) proposed that social deficits and stereotyped behaviors in autism arise from dysfunctional mesocorticolimbic and nigrostriatal dopamine systems, respectively. This theory is supported by studies that reveal both social and monetary reward processing deficits in autism (Schmitz et al., 2008; Scott-Van Zeeland et al., 2010). In fact, social reward learning has been linked to reduced activity in the ventral striatum in autism (Scott-Van Zeeland et al., 2010). Furthermore, a positron emission tomography (PET) imaging study by Ernst et al. (1997) reports reduced dopamine signaling in the mPFC during a theory of mind task. Genetic studies have also found polymorphisms in the genes for D1 (Hettinger et al., 2008), D2 (Hettinger et al., 2012), D3 (Staal et al., 2015), and D4 dopamine receptor subtypes (Gadow et al., 2010) in autistic individuals and families. Additionally, these polymorphisms have been related to the severity of stereotyped behaviors and differences in striatal volume (Staal et al., 2015), as well as to the severity of oppositional defiant disorder and separation anxiety in autistic children (Gadow et al., 2010). This body of evidence suggests that midbrain dopamine dysfunction likely contributes to several key
symptomatic behaviors in autism and could also underlie humor processing deficits in this population.

Dopamine dysfunction has been implicated in schizophrenia for decades, with the present-day hypothesis suggesting that dopamine hyperactivity in the DS, coupled with dopamine hypoactivity in the PFC and VS contributes to cognitive symptoms (Abi-Dargham & Grace, 2011; Perez-Costas et al., 2010; Weinstein et al., 2016). Neuroimaging studies have supported this theory. For example, a meta-analysis of PET imaging studies showed that on average, schizophrenia patients experience 14% greater dopamine synthesis capacity in the DS compared to controls (Fusar-Poli & Meyer-Lindenberg, 2013). This is supported by fMRI studies that demonstrate elevated activity in the DS of schizophrenic patients during episodes of psychosis compared to controls (Sorg et al., 2013). Aberrant reward processing is also evident in schizophrenia; patients demonstrate decreased VTA and VS activity during reward learning (Juckel et al., 2006; Morris et al., 2012; Rausch et al., 2014; Schlagenhauf et al., 2009), as well as in response to appetitive cues (Grimm et al., 2012). Reduced D1 receptor binding has also been revealed in the PFC of schizophrenic patients compared to controls. This likely underlies cognitive symptoms associated with reduced activity in PFC regions for this patient group (Okubo et al., 1997). For example, schizophrenic patients demonstrate lower activity relative to controls in the dorsolateral PFC and right MFG during the inhibition of prepotent responses (Holmes et al., 2005; A. W. MacDonald & Carter, 2003), as well as in the right amygdala, bilateral hippocampus, mPFC, caudate, putamen, midbrain, and thalamus while viewing unpleasant images (Takahashi et al., 2004). Therefore, it is likely that dysfunctional dopamine signaling throughout the striatum and PFC, coupled with cognitive and affective symptoms, underlie problems with comprehension and appreciation of humor in schizophrenic patients.

1.3 Parkinson’s disease (PD)

Although there is evidence implicating dopamine as an important neurotransmitter in humor processing, very little research on humor in Parkinson’s disease (PD) has been conducted, despite it being a dopamine-related disease. PD is a neurodegenerative disorder characterized by a progressive deterioration of dopaminergic neurons in the basal
ganglia (Yarnall et al., 2012). It is often recognized by its hallmark motor symptoms, including bradykinesia, resting tremor, rigidity, and postural instability (Okun et al., 2009). Several non-motor features of the disease have also been recently identified, including cognitive impairment, autonomic dysfunction, and psychiatric complaints (Okun et al., 2009). Socioemotional symptoms are also being increasingly recognized, including deficits in facial emotion recognition (e.g., Sprengelmeyer et al., 2003), emotional expression (e.g., Simons et al., 2003, 2004), and prosody detection (Buxton et al., 2013). In fact, some contend that the impact of non-motor and socioemotional symptoms on quality of life in PD is far greater than that of the disease’s motor symptoms (Morimoto et al., 2003)

1.3.1 Anatomy and function of the basal ganglia

The basal ganglia regulate motor behavior through two main circuits (Figure 1). In the direct pathway, the striatum sends inhibitory (i.e., GABAergic) signals to the internal segment of the global pallidus (GPi). The GPi’s default state is to inhibit the thalamus, so inhibition of the GPi leads to net excitation of the thalamus and release of glutamate throughout the cortex. In the motor cortex, this results in an increase in voluntary movement. The indirect pathway involves inhibitory projections from the striatum to the external segment of the global pallidus (GPe). The GPe typically inhibits the subthalamic nucleus (STN), which in turn excites the GPi. Therefore, inhibiting the GPe leads to a net increase in GPi activity via the excitatory STN. Recalling that the GPi normally inhibits the thalamus, the indirect pathway results in a net inhibition of the thalamus. This results in less excitatory signals being sent from the thalamus to the cortex, such as suppression of unwanted movements by the motor cortex. The GABAergic medium spiny neurons (MSNs) in the striatum are regulated through dopamine from the substantia nigra pars compacta (SNc) and VTA. Dopamine acts on MSN D1 receptors to excite the direct pathway and through MSN D2 receptors to inhibit the indirect pathway (Haber, 2016; Okun et al., 2009). In general, the SNc and VTA provide dopamine to the DS (i.e., majority of caudate and putamen), and VS (i.e., ventral caudate/putamen and NAcc), respectively (Perrone-Capano et al., 2008).
In the direct pathway, the striatum (NAcc, caudate, and putamen) releases inhibition of the thalamus by inhibiting the GPi, leading to a net increase in thalamic excitatory signaling to the cortex. In the indirect pathway, the striatum releases inhibition of the STN by inhibiting the GPe. The STN excites the GPi, leading to greater inhibition of the thalamus and a net decrease in thalamic excitatory signaling to the cortex. Dopamine increases and decreases activity of the striatum in the direct and indirect pathways, respectively. dACC = dorsal anterior cingulate cortex; dmPFC = dorsomedial prefrontal cortex; GPe = external segment of globus pallidus; GPi = internal segment of globus pallidus; MC = motor cortex; NAcc = nucleus accumbens; OFC = orbitofrontal cortex; PreMC = premotor cortex; SNc = substantia nigra pars compacta; STN = subthalamic nucleus; vmPFC = ventromedial prefrontal cortex; VTA = ventral tegmental area.
The striatum as a whole represents the main cortical input region of the basal ganglia. Cortical input to the striatum is arranged topographically, with motor and premotor cortices projecting to the putamen, dorsal prefrontal and anterior cingulate cortices projecting to the caudate, and the ventral medial and orbitofrontal cortices projecting to the NAcc (Figure 1; G. E. Alexander et al., 1986; Haber, 2016; Lehéricy et al., 2004). The DS is largely responsible for the planning and execution of voluntary goal-directed behaviors, which is supported by its demonstrated role in planning and executing volitional movement (Barbera et al., 2016; Kermadi & Boussaoud, 1995), inhibition of pre-potent responses (Ali et al., 2009; Robertson et al., 2015; X. Q. Yang et al., 2018), and performance of learned behaviors (Hiebert et al., 2017; Hiebert, Vo, et al., 2014). On the other hand, the VS mediates and guides these behaviors through emotional and motivational influence, demonstrated by its role in reward-based learning (Hiebert, Vo, et al., 2014; Vo et al., 2016), emotional recognition (Monk et al., 2008; Mühlberger et al., 2011), and temporal discounting (Hariri et al., 2006; McClure et al., 2004).

1.3.2 Pathology of PD

Early in PD, neurodegeneration begins in the SNc, resulting in the death of approximately 30% of dopaminergic neurons in this region by the time of motor symptom onset (Fearnley & Lees, 1991; Greffard et al., 2006). As the disease progresses, other dopaminergic nuclei become affected, including the VTA (Alberico et al., 2015). In PD, reductions in dopamine in the DS (due to early degeneration of the SNc) results in overactivation of the indirect pathway, making it difficult for patients to execute and control movements.

PD is also associated with the accumulation of misfolded α-synuclein protein aggregates in the brain (i.e., Lewy bodies). The Braak model suggests that the spreading of Lewy bodies throughout the brain occurs in a non-random fashion, proceeding through a series of six stages (Braak & Del Tredici, 2009). The first stage involves development of Lewy bodies in the dorsal motor nucleus of the vagus nerve and olfactory bulb, followed by specific areas of the medulla oblongata (i.e., raphe nucleus, reticular formation, and coeruleus) in the second stage. In the third stage, Lewy bodies have
reached the SNc. In stage four, the amygdala and thalamus become affected. Finally, in stages five and six, the cortex becomes affected (Braak & Del Tredici, 2009).

### 1.3.3 Treatment of PD

Currently, there is no cure for PD, so treatment strategies aim to manage symptoms. The ‘gold standard’ therapy is oral l-3,4-dihydroxyphenylalanine (i.e., l-DOPA), which is a precursor to dopamine. Levodopa capsules typically contain 100 mg l-DOPA and 25 mg of carbidopa, which inhibits peripheral metabolism of l-DOPA before it crosses the blood brain barrier. Once l-DOPA is taken up by neurons, it is converted into dopamine by the aromatic l-amino acid decarboxylase enzyme. Levodopa has a short half-life of approximately 1.5 hours (Salat & Tolosa, 2013), so many patients take multiple capsules per day. Repletion of dopamine through levodopa medication restores balance to the direct and indirect pathways of the basal ganglia and is an effective treatment for the motor symptoms of PD, particularly early in the disease. Over time, chronic levodopa administration can result in motor complications such as dyskinesia (Ko et al., 2014; Okun et al., 2009; Salat & Tolosa, 2013), however the exact mechanism for this is currently unknown (Pandey & Srivanitchapoom, 2017).

Dopamine agonists (e.g., rotigotine, pramipexole, apomorphine) can also be prescribed for PD. These agents mimic dopamine, primarily at striatal MSN D2 receptors that mediate the indirect pathway, resulting in decreased inhibition of thalamocortical signaling (Suski & Stacy, 2013). However, this can lead to unintended consequences for some PD patients, such as impulse control disorders (H. D. Weiss & Pontone, 2014).

Recent technological advances have led to the development of deep brain stimulation (DBS) surgery treatment for PD. This surgery involves implantation of electrical probes that provide direct stimulation to a particular area of the basal ganglia. The most common target is the STN (Groiss et al., 2009; Lyons et al., 2013). Due to the risks and costs of DBS surgery, it is only recommended for younger individuals with idiopathic PD who respond to levodopa yet have severe motor complications that are difficult to manage through medication. Outcomes of STN-DBS therapy are generally quite positive and long-lasting (Lyons et al., 2013).
1.3.4 Dopamine overdose hypothesis

In addition to its beneficial effects for motor symptoms, the pharmacological management of PD through levodopa restores cognitive abilities mediated by the DS, including cognitive flexibility (Aarts et al., 2014; Cools et al., 2001, 2003) and response selection (Hiebert et al., 2019; Vo et al., 2014). However, there are many cognitive symptoms of PD that do not respond as well to (and can even be worsened by) dopaminergic medication. The dopamine overdose hypothesis (Figure 2) suggests that there is a range of dopamine concentrations that contribute to optimal functioning, but that performance declines as concentrations become too low, or too high. In other words, areas of the brain that are spared in PD (e.g., VTA/VS early in the disease) are actually oversaturated with dopamine upon administration of levodopa and subsequently become dysfunctional (A. A. MacDonald et al., 2013; P. A. MacDonald & Monchi, 2011; Meder et al., 2019; Vaillancourt et al., 2013). This is supported by studies that demonstrate impairments in VS-mediated reward-based learning after levodopa administration in healthy young adults (Vo et al., 2016, 2017), healthy elderly adults (Vo et al., 2018), and PD patients (Aarts et al., 2014; Cools et al., 2001; Gotham et al., 1988; Graef et al., 2010; Hiebert, Seergobin, Vo, Ganjavi, & Macdonald, 2014; Vo et al., 2014). Furthermore, PD patients also show worsened cognitive impulsivity, operationalized as more risky betting strategies in gambling tasks, while ON levodopa (Cools et al., 2003; Torta et al., 2009). Finally, fMRI studies have shown that for PD patients ON levodopa, activity in the VS negatively correlates with reward learning (Aarts et al., 2014; Cools et al., 2007), and that the VS demonstrates less functional connectivity with the ACC and vmPFC (W. Yang et al., 2016).
Figure 2: Dopamine overdose hypothesis.
Neurodegeneration in PD causes dopamine depletion in the dorsal striatum (DS) that leads to decreased performance. Levodopa administration restores function in the DS to optimal levels. However, levodopa administration decreases function of the relatively spared ventral striatum (VS) via dopamine overdose. Adapted from Meder et al. (2019).
1.4 Humor processing in PD

There are several reasons to believe that humor processing would be dysfunctional in PD. First, humor comprehension and appreciation seem to involve an array of cortical and subcortical regions that are affected by PD. In other words, the disease itself likely causes disruptions to the brain’s humor processing ‘hardware’. Second, PD involves a variety of cognitive symptoms that humor processing relies on. This is analogous to disruptions in the brain’s humor processing ‘software’. For example, PD patients have demonstrated difficulties with lexical ambiguity processing, such as being unable to activate contextually appropriate ambiguous word meanings (Copland et al., 2000, 2001) and problems with inhibiting prepotent responses during word selection paradigms (Castner et al., 2007; Copland, Sefe, et al., 2009). This would of course have implications for verbal humor comprehension, particularly for puns, in which both meanings of an ambiguous word must be simultaneously activated. Third, pathological dopamine overdose in the VS with levodopa administration could lead to reductions in humor appreciation in PD patients, particularly for those early in the disease course. The VS has a demonstrated role in reward processing and becomes activated during the appreciation of humorous jokes. The dopamine overdose hypothesis would suggest that during PD patients’ medicated state, these functions would also become disrupted. In other words, although a patient might understand a joke, they might not find it funny. This could have profound impacts on the patient’s social interactions and quality of life. Based on these points, it is surprising that so few studies have been conducted on humor processing PD. To our knowledge, there are only three studies that have investigated humor in this disease population.

Benke et al. (1998) conducted a humor detection task with healthy elderly controls and PD patients with cognitive impairment (PDCI) and without cognitive impairment (PDnCI), determined by performance on the Münchner Gedächtnistest of verbal memory. Participants were shown a series of three similar cartoons and were asked to identify which one was humorous. Across 10 trials, PDCI patients performed significantly worse than the PDnCI and healthy elderly control groups. The PDCI patients’ accuracy rate was approximately 65%. There was no significant difference between the PDnCI group and
healthy elderly controls (i.e., both groups performed at around 80% accuracy rate). Furthermore, the authors found that performance on this cartoon-based humor task correlated positively with performance on the Raven Progressive Matrices tests that assess visuospatial abilities.

Thaler et al. (2012) conducted a multimodal investigation of humor processing in PD. Healthy elderly controls and PD patients were asked to rate how funny (on a scale of 0 = not funny at all to 4 = very funny) they found humorous video clips, cartoons, and audio sketches. Participants also completed the six-item Sense of Humor Questionnaire (SHQ-6). Across all three presentation methods, PD patients provided significantly lower funniness ratings compared to healthy controls. Furthermore, PD patients had lower scores than controls on the SHQ-6. Upon examination of clinical measures, a negative correlation between SHQ-6 score and disease severity was identified.

Finally, Mensen et al. (2014) investigated event-related potentials in PD patients and healthy young controls during a time estimation task using humorous pictures as a reward for correct responses. Throughout electroencephalography (EEG) recordings, participants were instructed to estimate durations of either 1, 2, or 5 seconds using a button press after trial initiation was indicated by the appearance of a neutral picture. If they provided a correct estimation (within a certain window of time that was adaptively based on task performance), a humorous alteration of the picture would be shown. PD patients showed similar early ERP activation patterns to controls, indicating spared visual processing. However, PD patients showed reductions in activation patterns in right-fronto-central areas around 270 msec post-feedback, compared to healthy controls. The authors suggest that this is evidence for dysfunctional reward processing in PD.

These prior studies (Benke et al., 1998; Mensen et al., 2014; Thaler et al., 2012) have several limitations. Most importantly, all three studies only tested PD patients while they were ON their regular dopaminergic medication, precluding a further understanding of the effects of dopaminergic therapies on humor processing in PD. Whether humor processing is impacted by dopamine overdose is impossible to determine from these studies. Another major limitation is that these studies did not distinguish between humor comprehension and appreciation, which are two distinct processes likely mediated by
separate neural pathways, and that could be affected differently by PD and dopaminergic therapy. The study by Benke et al. (1998) seems to approximate humor comprehension by asking participants to select the amusing picture. However, performance on this task inherently depends on what participants find subjectively ‘amusing’. Similarly, Thaler et al. (2012) only assessed humor appreciation by obtaining funniness ratings for their stimuli. However, humor appreciation is often reduced if the joke is not comprehended in the first place, so a low funniness rating could either mean that the participant did not understand the joke, or that they did not find the joke funny. Finally, Mensen et al. (2014) did not assess humor comprehension or appreciation at all, instead using humorous pictures as rewarding stimuli in a time estimation task.

1.5 Present Study

The present study aims to conduct the first thorough investigation into humor processing in PD by evaluating verbal humor comprehension and appreciation in PD patients and healthy elderly controls both ON and OFF levodopa medication. This is an essential first step in elucidating the potential presence and nature of humor processing deficits in PD and can provide important insights for future studies. Importantly, we use the trichotomous response profile proposed by Campbell et al. (2015) in which participants may indicate whether they comprehend a joke without necessarily appreciating it. This addresses one of the major limitations in prior humor research and allows us to distinguish between the separate processes of humor comprehension and humor appreciation. Furthermore, this study provides a unique opportunity to investigate the role of dopamine in humor processing by studying both PD patients and healthy controls in their normal (PD ON, control OFF) and altered (PD OFF, control ON) states.

1.5.1 Hypotheses

Previous evidence suggests that PD causes disruptions in DS-mediated lexical ambiguity processing (e.g., Castner et al., 2007; Copland et al., 2000) and response selection (e.g., Hiebert et al., 2019), which we believe will predispose PD patients to difficulties in comprehending verbal humor. Therefore, we predict that PD patients will
be worse at humor comprehension, especially for stimuli containing ambiguous words (i.e., puns), compared to healthy elderly controls, particularly when OFF medication.

Furthermore, the dopamine overdose hypothesis suggests that VS-mediated processes such as reward-based learning (e.g., Cools et al., 2006; Hiebert, Seergobin, et al., 2014), become dysfunctional with levodopa administration. We believe that humor appreciation, a VS-mediated response to subjectively amusing jokes, will similarly be affected by levodopa-induced dopamine overdose. We therefore predict that both PD patients and healthy elderly controls will find jokes less humorous while ON levodopa. This would confirm and expand upon the findings from Thaler et al. (2012), in which PD patients ON dopaminergic medication rated cartoon, video, and auditory humor as significantly less funny compared to unmedicated healthy controls.
Chapter 2

2 Methods

2.1 Participants

Based on an alpha of .05, and an effect size estimate of $f = .25$, an a priori power analysis (calculated using G*Power v. 3.1; Faul et al., 2009) suggested that approximately 34 participants (i.e., 17 per group) would be required to achieve sufficient power of .80 in a repeated measures mixed ANOVA (Cohen, 1988). Ten PD patients and 10 healthy elderly control participants, matched for age and sex, participated in this study. Due to circumstances surrounding the COVID-19 pandemic, we were unable to achieve our target sample size. However, this smaller sample size is considered sufficient for the exploratory nature of this study, and the current study aims to provide explicit effect sizes that could be used for future, well-powered studies. All participants provided written and informed consent (Appendix A) according to the Declaration of Helsinki (1991) and all procedures were approved by the Research Ethics Board at the University of Western Ontario (London, Ontario, Canada; Appendix B).

PD patients were diagnosed by a licensed movement disorders neurologist using UK Brain Bank and Movement Disorder Society (MDS) criteria and were medically managed on stable dopamine replacement therapy (e.g., levodopa) for at least 3 months. All participants were screened for cognitive impairment and major depression/anxiety. The MDS-Unified Parkinson’s Disease Rating Scale Motor Subscale (MDS-UPDRS III; Goetz et al., 2008) was conducted at each session for all participants to evaluate PD severity and rule out motor impairments in controls. Control participants were also screened to rule out contraindications for levodopa administration (e.g., persistent hypotension, glaucoma).

2.2 Procedures

All participants took part in two experimental sessions; ON and OFF levodopa. Medication order was counter-balanced across participants. PD patients were instructed to either take their prescribed dopaminergic medication normally (ON), or abstain from their
medication prior to the session (OFF). Specifically, PD patients were instructed to abstain from dopamine precursors (e.g., levodopa), aromatic-L-amino-acid decarboxylase inhibitors (e.g., carbidopa), and catechol-O-methytransferase (COMT) inhibitors (e.g., entacapone) for 12-16 hours; additionally, they were asked to abstain from dopamine precursors such as pramipexole (Mirapex), ropinirole (Requip), pergolide (Permax), amantadine (Symmetrel), rasagiline (Azilect) and selegiline (Eldepryl/Deprenyl) for 16-20 hours prior to testing. Controls were administered a capsule at each session, containing either 100mg levodopa + 25mg carbidopa (ON), or a cornstarch placebo (OFF), in a single-blinded manner.

At the first session, participants gave written, informed consent to participate in the study (Appendix A) and completed a health and demographics form (Appendix C). Additionally, control participants completed the Levodopa Safety Screening Questionnaire (Appendix D) to evaluate preparedness for levodopa administration. At the start of each session, sitting and standing blood pressure measurements were obtained for a baseline. Control participants were next instructed to swallow a capsule that contained either 100mg levodopa + 25mg carbidopa (ON) or cornstarch (OFF), depending on the counterbalanced medication order they had been assigned prior to the study. Control participants were blinded to these conditions throughout the study. After ingestion of the capsule, control participants underwent a 45-minute waiting period in order for levodopa to reach maximal plasma levels. Sitting and standing blood pressure measurements were obtained once more at the end of the 45-minute waiting period.

At the end of each session, final sitting and standing blood pressure measurements were recorded. Participants also completed the MDS-UPDRS III (Goetz et al., 2008) at this time, which was video recorded to be scored by a licensed movement disorders neurologist at a later date. At the second session, all participants were compensated with $75.00 CAD in cash in appreciation for their time commitment to the study. In order to assess whether potentially noticeable side effects had unblinded control participants, they were asked at the second session to indicate which session they believed they had received the active levodopa capsule. Following this, control participants were debriefed about medication order.
2.2.1 Questionnaires and Assessments

Across the two experimental sessions, participants completed a variety of questionnaires and assessments. Those that relied on cognitive ability were administered during “normal state” sessions (i.e., controls OFF; PD ON) in an effort to maintain optimal level of functioning during these assessments. In addition to the questionnaires outlined below, the Epworth Sleepiness Scale (ESS, Appendix E; Johns, 1991) and Barratt Impulsiveness Scale (BIS, Appendix F; Patton et al., 1995) were collected for comparison purposes with a larger sample of PD patients and were not included in the present analyses. Measures of mood and affect were obtained at both ON and OFF sessions after peak plasma levels of levodopa had been reached in order to evaluate whether an effect of levodopa was present.

2.2.1.1 Bond & Lader Visual Analogue Mood Scale (BL-VAS)

At the start of each session (directly following capsule administration for controls) participants completed the Bond & Lader (1974) visual analogue mood scale (BL-VAS; Appendix G). Participants also completed a second BL-VAS at the end of each session (i.e., at peak plasma levodopa levels). The BL-VAS contains sixteen 100 mm scales with opposing adjectives at either end (e.g., “Alert – Drowsy”). Participants were asked to imagine each end of the scale as representing the most of that adjective that they had ever felt in their life and put a vertical line through the scale indicating how they felt at the present moment. The BL-VAS is scored by measuring (in mm) the distance between the participant’s mark and the left-most end of the scale. Half of the items are reverse scored (i.e., subtracted from 100 mm) in order to remove handedness bias. The BL-VAS contains three subscales: Alert (9 items), Contented (5 items), and Calm (2 items). Subscale scores are calculated as an average of the mm scores for each of the subscale items. Several studies have demonstrated that the BL-VAS is sensitive to changes in subjective effects of drugs such as chlorogenic acid (Camfield et al., 2013), lorazepam (Schunk et al., 2011), and tetrahydrocannabinol (Kleinloog et al., 2014). In the present study, the BL-VAS was used to assess any subjective changes in mood following levodopa administration.
2.2.1.2 Montreal Cognitive Assessment (MoCA)

During “normal state” sessions (controls OFF; PD ON), participants’ cognitive ability was assessed using the Montreal Cognitive Assessment (MoCA, Appendix H; Nasreddine et al., 2005). The MoCA is a widely-used cognitive screening tool that has been validated and recommended for use in evaluating mild cognitive impairment in PD (Hoops et al., 2009; Skorvanek et al., 2018). The MoCA is scored out of 30, and contains items testing a variety of cognitive functions, including visuospatial abilities (e.g., clock drawing), short-term memory recall, executive functions (e.g., verbal abstraction), attention, language, and orientation to time and place. Participants were included in the present study if their MoCA score was above 23. Although this is below the traditional MoCA cut-off of 26 for mild cognitive impairment, a recent review suggests that a cut-off of 23 is more appropriate, particularly for those of older age (Carson et al., 2018).

Not only were MoCA scores were used to screen for mild cognitive impairment in participants, we also sought to investigate the whether MoCA scores could predict humor comprehension, as previous studies suggest that cognitive ability contributes to humor comprehension (Benke et al., 1998; Shammi & Stuss, 2003). For example, scores on the Mini Mental State Examination (a similar assessment of cognitive function to the MoCA) have been shown to mediate the relationship between age and humor comprehension ability in the elderly (Daniluk & Borkowska, 2017). Furthermore, PD patients with reduced sense of humor (i.e., lower SHQ-6 scores) demonstrate difficulties on the executive function portion of the MoCA (Thaler et al., 2012).

2.2.1.3 American version of the Nelson Adult Reading Test (AMNART)

At “normal state” sessions (controls OFF; PD ON) premorbid verbal IQ was estimated using the American version of the Nelson Adult Reading Test (AMNART, Appendix I; Grober & Sliwinski, 1991). The AMNART is adapted from the original National Adult Reading Test (NART; Nelson, 1982) and asks participants to read aloud 50 words whose pronunciation is not intuitive from the spelling (e.g., thyme). The AMNART is scored by giving one point per incorrectly pronounced word. To estimate premorbid IQ, the number of incorrectly pronounced words and the participant’s years of
education are entered into the following equation: 118.2 – 0.89(AMNART errors) + 0.64(years of education). This measure has been shown to be a good estimate of current verbal IQ measured with the revised Wechsler Adult Intelligence Scale (WAIS-R) in a sample of nondemented elderly participants (Grober & Sliwinski, 1991). It was also found to be an acceptable predictor of full-scale IQ measured with the WAIS in a sample of 65 university undergraduate students (Collins, 1999). Several studies have implicated a relationship between verbal or full-scale IQ and humor comprehension ability (Brown et al., 2005; Feingold & Mazzella, 1991; Wierzbicki & Young, 1978).

2.2.1.4 Six-item Sense of Humor Questionnaire (SHQ-6)

In order to account for individual differences in sense of humor, the SHQ-6 (Appendix J; Svebak, 1996) was administered to participants. The SHQ-6 is a shortened version of the revised SHQ (SHQ-R; Svebak, 1974) that contains six questions related to sensitivity to meta-messages (e.g., “Do you easily recognize a hint like a twinkle or a slight change in emphasis as a mark of humorous intent?”) and liking of humorous situations and individuals (e.g., “Persons who are always out to be funny are really irresponsible types not to be relied upon”). Participants respond to these questions using a 4-point scale. The SHQ-6 is scored by summing the points across all questions, with higher values indicating a greater sense of humor. In its original validation study (Svebak, 1996), the SHQ-6 was shown to be positively correlated to the SHQ-R and general life regard (measured with the Life Regard Index), and negatively correlated with depression scores (measured with the Zung Depression Scale).

For the present study, we chose to use the SHQ-6 instead of other humor scales such as the widely-used Humor Styles Questionnaire (HSQ; Martin et al., 2003) because the SHQ-6 focuses on humor comprehension and appreciation abilities rather than on one’s own use or production of humor. Furthermore, the SHQ-6 was used in one of the few studies that evaluated humor in PD (Thaler et al., 2012).

2.2.1.5 Twenty-item Toronto Alexithymia Scale (TAS-20)

In order to evaluate the effects of potential emotional deficits induced by PD on humor processing, all participants completed the Toronto Alexithymia Scale (TAS-20,
Appendix K; Bagby et al., 1994). Alexithymia reflects an inability to describe one’s own feelings or emotions. Several studies have demonstrated that alexithymia is present in PD at nearly double the rate of healthy elderly populations (Assogna et al., 2016; Costa et al., 2010; Costa & Caltagirone, 2016). Furthermore, alexithymia has been associated with deficits in humor processing, with some evidence suggesting that a common mechanism could induce alexithymia and humor deficits in certain populations (Patrikelis et al., 2017, 2019).

The TAS-20 consists of three factors: 1) Difficulty Identifying Feelings (e.g., “I am often confused about what emotion I am feeling”), 2) Difficulty Describing Feelings (e.g., “It is difficult for me to find the right words for my feelings”), and 3) Externally-Oriented Thinking (e.g., “I prefer to analyze problems rather than just describe them”). Participants respond to these questions with a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Scoring for 5 items is reversed. Factor scores are calculated by summing the responses for items within each factor. A total score is also generated, which can be used with cut-offs to identify individuals with high (≥ 61) or low (≤ 51) alexithymia. The TAS-20 is widely used and has demonstrated adequate reliability and validity across languages and cultures (R. M. Bagby et al., 2020; Taylor et al., 2003).

2.2.1.6 Oxford Happiness Questionnaire (OHQ)

The Oxford Happiness Questionnaire (OHQ, Appendix L; Hills & Argyle, 2002) was collected to gain a measure of general happiness. The OHQ includes 29 statements about personal happiness (e.g., “I often experience joy and elation”) that participants respond to using a 6-point Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree). Twelve of the items are reverse scored. An overall score for the OHQ is generated by averaging responses across all of the items. A higher score indicates greater levels of happiness. Several studies have demonstrated a relationship between scores on the OHQ and “self-enhancing humor” and “affiliative humor” styles of humor, suggesting that happy people tend to adopt more positive humor styles (Ford et al., 2016; Yaprak et al., 2018).
2.2.1.7  Beck Depression Inventory II (BDI-II)

At the end of each session (i.e., after plasma levels of levodopa had reached its peak), participants completed the Beck Depression Inventory II (BDI-II; Beck et al., 1996) to assess depressive symptoms. The BDI-II is a 21-item self-report of depressive symptoms experienced over the past two weeks (e.g., “sadness”, “crying”). Participants respond using a 4-point scale ranging from 0 (no experience of depressive symptoms) to 3 (frequent experience of depressive symptoms). The BDI-II is scored by summing these responses (scores range from 0-63), with higher scores indicating greater levels of depression. Cut-off scores range from 0-13 (minimal depression), 14-19 (mild depression), 20-28 (moderate depression), and ≥ 29 (severe depression).

PD patients suffer from depression at higher rates than the general population, with an approximate prevalence of at least 20% (Burn, 2002; Goodarzi et al., 2016; Martínez-Martín & Damián, 2010; Poewe, 2007; Schwarz et al., 2011). The BDI-II is considered to be an excellent measure of the presence and severity of depression in PD, and the MDS has recommended the use of the BDI-II in PD populations (Schrag et al., 2007; Visser et al., 2006).

2.2.1.8  Beck Anxiety Inventory (BAI)

The Beck Anxiety Inventory (BAI; Aaron T. Beck et al., 1988) was also administered to participants at the end of each session to assess anxiety symptoms. The BAI contains 21 physical and mental symptoms of anxiety (e.g., “Numbness or tingling”, “Fear of the worst happening”) and asks participants to rate how bothered they have been by each symptom in the past week using a 4-point scale from 0 (not at all) to 3 (severely). The BAI is scored by summing these items (scores range from 0-63), with greater scores indicating higher levels of anxiety. Cut-off scores range from 0-7 (minimal anxiety), 8-15 (mild anxiety), 16-25 (moderate anxiety), and ≥ 26 (severe anxiety).

Clinically significant anxiety is reported to be present in approximately 30% of PD patients (Broen et al., 2016; Dissanayaka et al., 2010; Mele et al., 2018). However, there are currently no anxiety rating scales that have been recommended for use by the
MDS (Leentjens et al., 2015). The MDS has determined that the BAI fulfils the criteria for “suggested” use in PD.

2.2.1.9 **Starkstein Apathy Scale (SAS)**

At the end of each session, the Starkstein Apathy Scale (SAS, Appendix M; Starkstein et al., 1992) was also collected to assess clinical apathy within our participants. The SAS contains 14 items regarding motivation and interest, such as “Are you interested in learning new things?”. Participants respond using a 4-point scale ranging from 0 (not at all) to 4 (a lot). Six of the items are reverse scored, and the scale is summed for a final SAS score (range from 0-42), with higher scores indicating greater levels of apathy. A cut-off score of 14 is suggested for distinguishing between those with (≥ 14) and without (< 14) apathy.

Approximately 30-40% of PD patients are reported to have apathy (Den Brok et al., 2015; Mele et al., 2019; Pagonabarraga et al., 2015; Pedersen et al., 2012; Starkstein & Brockman, 2011). The SAS has demonstrated excellent reliability and validity, and is currently the only apathy scale that is “recommended” by the MDS for use in PD populations (Leentjens et al., 2008).

2.2.1.10 **New Freezing of Gait Questionnaire (N-FOG)**

The New Freezing of Gait questionnaire (N-FOG, Appendix N; Nieuwboer et al., 2009) was administered to PD patients only to assess freezing of gait symptoms. Freezing of gait is a common symptom of PD in which the patient suddenly experiences disruption in walking, accompanied by a feeling that the feet are “glued” to the floor. These episodes often occur during the initiation of movement, while turning, or when walking through narrow spaces. Freezing of gait is often associated with greater disease severity, and is experienced by approximately 40% of PD patients (Perez-Lloret et al., 2014). The 9-item N-FOG assesses the presence, severity, and functional impact of freezing of gait over the past month. If the patient has not experienced a freezing episode during this time, they are given a score of 0. Patients who have experienced freezing can receive total scores ranging from 1-29, with higher scores indicating greater severity and functional impact of freezing.
2.2.2 Humor Processing Task

At each session, participants completed a humor processing task that involved listening to audio clips ranging in duration from 3-13 seconds (see Appendix O for written list of auditory stimuli). Half of the audio clips were jokes and the other half were neutral (i.e., non-jokes). Furthermore, half of the audio clips involved ambiguity in the form of a play on word. These words were either homophones (e.g., toad vs. towed), or homonyms (e.g., bar as in a metal pole vs. bar as in a drinking establishment). Jokes containing ambiguous words were considered to be puns. The majority of the stimuli (92) have been used in previous studies (Bekinschtein et al., 2011; Fiacconi & Owen, 2015), although 68 additional stimuli were generated to increase the size of this stimulus database. The new stimuli followed the same structure as the previous set and were similar in duration. All 160 stimuli were recorded by a male voice and spoken as neutrally as possible, so as not to reveal whether the audio clip was a joke or non-joke solely based on intonation. The audio was presented to participants through headphones. At the start of the task, a volume check was conducted to ensure that participants could properly hear the audio through the headphones.

At each session, participants were exposed to 80 audio clips with equal distributions of each audio clip type (i.e., 20 of each; unambiguous joke, unambiguous non-joke, ambiguous joke, ambiguous non-joke). No audio clips were repeated within or across sessions. The audio clips were presented in a random order for each PD patient and matched control pair. Following each audio clip, participants were asked to choose one of three categories for the clip: 1) not a joke, 2) joke – funny, or 3) joke – not funny. This trichotomous response profile was originally proposed by Campbell et al. (2015), and allows for the separation of humor comprehension and humor appreciation. For example, one could understand that an audio clip was intended to be a joke (i.e., demonstrating humor comprehension), but not experience amusement (i.e., failing to demonstrate humor appreciation), thus categorizing the clip as “joke – not funny”. This represents a major improvement from previous humor research, in which participants are often asked to categorize auditory jokes as either “funny”, or “not funny” (e.g., Chan et al., 2012; Goel & Dolan, 2001; Marinkovic et al., 2011; Mobbs et al., 2003), or are asked to simply rate
how funny each stimulus was (e.g., Bartolo et al., 2006; Bekinschtein et al., 2011; Chan, 2016; Cunningham & Derks, 2005; Fiacconi & Owen, 2015; Galloway & Chirico, 2008; Gutiérrez et al., 2018; Korb et al., 2012; Shultz, 1972; Thaler et al., 2012; Tian et al., 2017; Vrticka et al., 2013; Wild et al., 2006). Unfortunately, these prior methods prevent participants from demonstrating humor comprehension for jokes that they indeed understand, yet simply do not find funny.

In order to gain an index of humor appreciation beyond the categorization of an audio clips as a “funny joke”, participants were next asked to rate how funny the audio clip was on a scale from 1 (not funny at all) to 4 (extremely funny), regardless of whether the audio was a joke or non-joke, and also regardless of how participants had categorized it on the previous screen. Participants were instructed to make both categorization and rating responses using the up and down arrow keys on a standard keyboard to select their desired response. The selected response would be highlighted in green. The starting position of this green highlighted selection was randomized on each response screen, to prevent biases in response times (RT) for selections that were closer or further to the starting selection. Once participants had selected their response, they were instructed to press the space bar to confirm their answer. Participants had a maximum of 5 seconds to make each response (Figure 3). Prior to completing the task, all participants watched a video containing detailed instructions of the aforementioned procedure and were provided with an opportunity to ask questions for further clarification, if necessary.
Participants listened to an audio clip ranging from 3-13 seconds in length. Following this, they were asked to categorize the audio as either 1) joke – funny, 2) joke – not funny, or 3) not a joke. Next, they were asked to rate how funny the audio clip was, regardless of how it had been categorized previously. Participants had a maximum of 5 seconds to make each response. Participants used the up and down arrow keys on a standard keyboard to make their selection, which was highlighted in green, and confirmed their response with the space bar.

2.3 Statistical Analyses

All data were analyzed with R statistical computing software (v. 3.6.3) and R Studio (v. 1.1.463). Humor comprehension (i.e., categorization accuracy of correctly assigning jokes and non-jokes) and humor appreciation (i.e., average funniness ratings) data were examined for outliers above or below 3 x the interquartile range (IQR) for both PD and control groups. RT data for both humor comprehension and appreciation were also examined for time-out instances, in which participants failed to respond within the 5-second time limit. In all undermentioned statistical analyses, the assumptions of ANOVA were met, except for the assumption of normality in a few indicated cases. However, ANOVA is generally considered to be quite robust to moderate violations of the
normality assumption (Blanca et al., 2017; Glass et al., 1972). Because of these moderate normality violations, the Flinger-Killeen test, which is robust to departures from normality, was used to test for homogeneity of variance (Conover et al., 1981). Due to the exploratory nature of this study, and to conserve power, correction for multiplicity adjusting for the number of statistical tests was not conducted for our main outcome measures (Rothman, 1990; Streiner, 2015). As this study primarily represents an initial investigation into potential humor processing deficits in PD, our aim was to reduce Type II errors which could preclude well-powered follow-up studies. Where applicable (e.g., testing for baseline differences in demographic measures between PD and controls, levodopa effects on depression, anxiety, apathy, and mood scores), Bonferroni correction was used to adjust for multiple comparisons. All post hoc contrasts were conducted using estimated marginal means.

2.3.1 Demographic, clinical, and questionnaire measures

The difference between PD patients and controls was evaluated for all demographic and clinical measures (e.g., age, education) and questionnaires that were administered at a single session (e.g., SHQ-6, TAS-20) using independent sample t-tests, correcting for multiplicity using the Bonferroni method. Questionnaires that were administered at both sessions (e.g., BDI-II, VAS) were evaluated with 2 x 2 mixed ANOVAs, with Group (control vs. PD) as a between-subjects factor and Medication (OFF vs. ON) as a within-subjects repeated measures factor, using the Bonferroni method to adjust for multiple comparisons.

2.3.2 Humor Comprehension

Humor comprehension was measured as the percentage of joke and non-joke stimuli that were correctly categorized as such. Jokes were considered correct if participants chose either the “Joke – Funny” or “Joke – Not Funny” category. Non-jokes were only considered correct if the “Not a joke” category was selected. These humor comprehension scores were entered into a 2 x 2 x 2 x 2 mixed ANOVA, with Group (control vs. PD) as the between-subjects factor, and Medication (OFF vs. ON), Ambiguity
(unambiguous vs. ambiguous), and Stimulus Type (non-joke vs. joke) as the within-subjects factors.

In a previous study, Campbell et al. (2015) found that participants incorrectly categorized non-jokes more often than jokes. In order to assess whether this was an indication of worse humor comprehension (i.e., failing to recognize when a stimulus is not intended to be humorous) or greater humor appreciation (i.e., finding more stimuli humorous in general), they analyzed the number of incorrectly categorized non-jokes that were classified as either funny jokes or not funny jokes. We conducted a similar analysis, in which responding bias for incorrect non-jokes was assessed with normalized difference scores between “Joke – Funny” and “Joke – Not Funny” responses for non-joke stimuli. These data were entered into a 2 x 2 x 2 mixed ANOVA, with Group (control vs. PD) as a between-subjects factor, and Medication (OFF vs. ON) and Ambiguity (unambiguous vs. ambiguous) as within-subjects factors.

Next, the average RT for categorization of the stimuli as jokes or non-jokes was taken as a measure of humor comprehension latency. This measure was entered into a 2 x 2 x 2 x 2 mixed ANOVA, with Group (PD vs. control) as the between-subjects factor, and Medication (ON vs. OFF), Ambiguity (ambiguous vs. unambiguous), and Stimulus Type (joke vs. non-joke) as the within-subjects factors.

Finally, three separate multiple regression analyses were conducted to evaluate the relationships between humor comprehension (percent correct) and clinical, demographic, and affective factors. The first regression evaluated the effects of disease duration, levodopa equivalent dose (LED), and freezing of gait (N-FOG) scores on humor comprehension. The second regression evaluated the effects of age, years of education, cognitive ability (MoCA), estimated premorbid IQ (AMNART), happiness (OHQ), alexithymia (TAS-20), and sense of humor (SHQ-6) on humor comprehension. Finally, a third regression analysis evaluated the effects of depression (BDI-II), anxiety (BAI), and apathy (SAS) on humor comprehension.
2.3.3 **Humor Appreciation**

Humor appreciation was measured as the average funniness rating on our 4-point Likert-type scale (1 = not funny at all; 2 = mildly funny; 3 = moderately funny; 4 = extremely funny). Average funniness ratings were used as the outcome measure in a 2 x 2 x 2 x 2 mixed ANOVA, with Group (control vs. PD) as the between-subjects factor, and Medication (OFF vs. ON), Ambiguity (unambiguous vs. ambiguous), and Stimulus Type (non-joke vs. joke) as the within-subjects factors.

Responding bias for correctly identified jokes was also used as a measure of humor appreciation. This was calculated as the normalized difference score between “Joke – Funny” and “Joke – Not Funny” responses for correctly identified joke stimuli. These data were entered into a 2 x 2 x 2 mixed ANOVA. Once again, Group (control vs. PD) acted as the between-subjects factor, whereas Medication (OFF vs. ON) and Ambiguity (unambiguous vs. ambiguous) acted as within-subjects factors.

Next, RT for the funniness rating was taken as a measure of humor appreciation latency, and analyzed in a 2 x 2 x 2 x 2 mixed ANOVA, with Group (control vs. PD) as the between-subjects factor, and Medication (OFF vs. ON), Ambiguity (unambiguous vs. ambiguous), and Stimulus Type (non-joke vs. joke) as the within-subjects factors.

Lastly, three separate multiple regression analyses were conducted to evaluate the relationships between humor appreciation (average funniness rating) and clinical, demographic, and affective factors. The first regression evaluated the effects of disease duration, levodopa equivalent dose (LED), and freezing of gait (N-FOG) scores on humor appreciation. The second regression evaluated the effects of age, years of education, cognitive ability (MoCA), estimated premorbid IQ (AMNART), happiness (OHQ), alexithymia (TAS-20), and sense of humor (SHQ-6) on humor appreciation. Finally, a third regression analysis evaluated the effects of depression (BDI-II), anxiety (BAI), and apathy (SAS) on humor appreciation.
Chapter 3

3 Results

We first evaluated demographic, clinical and questionnaire measures for differences between groups and medication status. Then, humor comprehension was investigated using a) the overall percentage of correct responses, b) responding bias for incorrect non-joke trials, and c) RT as outcome measures. The relationship between humor comprehension scores (percent correct) and clinical, demographic/questionnaire, and affective measures was also examined. Finally, humor appreciation was evaluated by using a) average funniness rating, b) responding bias for correct joke trials, and c) RT as outcome measures. The relationship between humor appreciation (average funniness rating) and clinical, demographic/questionnaire, and affective measures was also analyzed. See Figure 4 for an overview of these analyses.

Figure 4: Overview of analyses.
Flow chart summarizing analysis process. RT = response time.
3.1 **Demographic, clinical, and questionnaire measures**

As shown in Table 1, PD patients and controls did not differ in age, education, cognitive ability (MoCA), premorbid IQ (estimated with the AMNART), sense of humor (SHQ-6), or alexithymia (TAS-20). Control participants reported significantly higher happiness scores on the OHQ compared to PD patients, $t(18) = 4.31, p < .01$.

**Table 1: Demographic, clinical, and questionnaire measures.**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=10)</th>
<th>PD (n=10)</th>
<th>t-test</th>
<th>Cohen’s D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.8 ± 5.12</td>
<td>71.3 ± 6.55</td>
<td>-1.33</td>
<td>0.60</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.1 ± 1.73</td>
<td>16.8 ± 1.75</td>
<td>-2.18</td>
<td>0.98</td>
</tr>
<tr>
<td>MoCA</td>
<td>28.8 ± 1.40</td>
<td>27.2 ± 1.99</td>
<td>2.08</td>
<td>0.93</td>
</tr>
<tr>
<td>AMNART</td>
<td>116.2 ± 8.54</td>
<td>117.7 ± 6.22</td>
<td>-0.46</td>
<td>0.21</td>
</tr>
<tr>
<td>SHQ-6</td>
<td>20.8 ± 2.70</td>
<td>18.6 ± 2.01</td>
<td>2.07</td>
<td>0.92</td>
</tr>
<tr>
<td>OHQ</td>
<td>5.06 ± 0.49</td>
<td>4.17 ± 0.44</td>
<td>4.31**</td>
<td>1.93</td>
</tr>
<tr>
<td>TAS-20</td>
<td>40.1 ± 10.16</td>
<td>43.5 ± 10.70</td>
<td>-0.73</td>
<td>0.33</td>
</tr>
<tr>
<td>Disease Duration (years)</td>
<td>— —</td>
<td>5.7 ± 4.69</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td>LED</td>
<td>— —</td>
<td>621.5 ± 322.92</td>
<td>— —</td>
<td>— —</td>
</tr>
<tr>
<td>N-FOG (n = 5)</td>
<td>— —</td>
<td>7.6 ± 8.46</td>
<td>— —</td>
<td>— —</td>
</tr>
</tbody>
</table>

*Note: Bonferroni-corrected independent t-tests were used to evaluate equality of means. M = mean; SD = standard deviation; MoCA = Montreal Cognitive Assessment; AMNART = American version of the Nelson Adult Reading Test; SHQ-6 = six-item Sense of Humor Questionnaire; OHQ = Oxford Happiness Questionnaire; TAS-20 = 20-item Toronto Alexithymia Scale; LED = levodopa equivalent dose; N-FOG = New Freezing of Gait Questionnaire. **$p < .01$*

Control participants’ ability to correctly identify their medication order was compared to chance levels with a one sample t-test. This was not significant ($t(9) = -0.61$, $p = .56$), suggesting that controls indeed remained blind to their medication order until debriefing.

### 3.1.1 Affective Measures

Depression (BDI-II), anxiety (BAI), and apathy (SAS) for both sessions and groups are shown in Table 2. A 2 x 2 mixed ANOVA for BDI-II scores demonstrated that PD patients ($M = 11.7$, 95% CI [8.39, 15.01]) were significantly more depressed than controls ($M = 1.3$, 95% CI [-2.01, 4.61]), regardless of medication status, $F(1,18) = 21.82, p < .001$, $\eta^2_p = .548$. 
Similarly, a 2 x 2 mixed ANOVA for BAI scores showed that PD patients ($M = 9.35$, 95% CI [6.47, 12.23]) were significantly more anxious than controls ($M = 0.95$, 95% CI [-1.93, 3.83]), regardless of medication status, $F(1,18) = 18.83$, $p < .001$, $\eta^2_p = .511$.

Finally, a 2 x 2 mixed ANOVA for SAS scores revealed a significant two-way interaction between Group x Medication, $F(1,18) = 8.92$, $p = .008$, $\eta^2_p = .331$. This was mainly driven by a significant simple main effect of Medication for PD patients only ($t(18) = -2.88$, $p = .01$), in which PD patients reported feeling more apathetic ON medication ($M = 16.9$, 95% CI [13.69, 20.11]) compared to OFF medication ($M = 14.1$, 95% CI [10.89, 17.31]).

Table 2: Affective measures for PD patients and controls OFF and ON levodopa.

<table>
<thead>
<tr>
<th></th>
<th>Control (n=10)</th>
<th>PD (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OFF</td>
<td>ON</td>
</tr>
<tr>
<td>BDI-II</td>
<td>1.1 (1.20)</td>
<td>1.5 (1.18)</td>
</tr>
<tr>
<td>BAI</td>
<td>0.9 (1.45)</td>
<td>1.0 (1.25)</td>
</tr>
<tr>
<td>SAS</td>
<td>8.5 (4.50)</td>
<td>7.2 (4.05)</td>
</tr>
</tbody>
</table>

*Note:* Mean values shown with standard deviation in parentheses. BDI-II = Beck Depression Inventory II; BAI = Beck Anxiety Inventory; SAS = Starkstein Apathy Scale.

3.1.2 Change in Mood over Session

To assess participants’ change in mood over each session, BL-VAS subscale scores from the beginning of the session were subtracted from the BL-VAS subscale scores obtained at the end of the session. More positive values represent an increase in a participant’s mood over the session, whereas negative values represent and decrease in mood. Data are shown in
Table 3 for both participant groups and medication state. In all but one case, participants reported less extreme mood values at the end of the sessions relative to the beginning of the sessions. Change scores for each of the BL-VAS subscales were entered into separate 2 x 2 mixed ANOVAs. No significant main or interaction effects of Group or Medication were found.
Table 3: Change in mood over session for PD patients and controls OFF and ON levodopa.

<table>
<thead>
<tr>
<th>BL-VAS Subscale</th>
<th>Control (n=10)</th>
<th>PD (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OFF</td>
<td>ON</td>
</tr>
<tr>
<td>Alertness</td>
<td>-6.94 (8.60)</td>
<td>-5.61 (8.90)</td>
</tr>
<tr>
<td>Calmness</td>
<td>-5.75 (10.80)</td>
<td>-6.10 (14.04)</td>
</tr>
<tr>
<td>Contentedness</td>
<td>-1.85 (3.88)</td>
<td>-5.61 (10.35)</td>
</tr>
</tbody>
</table>

Note: Mean values shown with standard deviation in parentheses. BL-VAS = Bond & Lader Visual Analogue Scale.

3.2 Humor Comprehension

Humor comprehension was measured as the percentage of stimuli correctly categorized as jokes or non-jokes. These data were assessed for outliers above or below 3 x IQR. No extreme values were identified. Data are shown in Table 4.

Table 4: Humor comprehension accuracy and response time (RT) in PD patients and controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>Medication</th>
<th>Ambiguity</th>
<th>Stimulus Type</th>
<th>Mean % correct</th>
<th>Mean RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=10)</td>
<td>OFF</td>
<td>Unambiguous</td>
<td>Joke</td>
<td>82.5 (12.30)</td>
<td>2600.16 (572.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>87.5 (9.79)</td>
<td>2125.58 (452.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous</td>
<td>Joke</td>
<td>84.5 (9.27)</td>
<td>2504.10 (606.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>64.5 (13.83)</td>
<td>2498.75 (450.11)</td>
</tr>
<tr>
<td></td>
<td>ON</td>
<td>Unambiguous</td>
<td>Joke</td>
<td>77.0 (18.74)</td>
<td>2600.30 (530.34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>89.5 (9.56)</td>
<td>2012.80 (446.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous</td>
<td>Joke</td>
<td>84.0 (11.74)</td>
<td>2400.30 (527.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>68.0 (16.19)</td>
<td>2363.54 (450.80)</td>
</tr>
<tr>
<td>Patient (n=10)</td>
<td>OFF</td>
<td>Unambiguous</td>
<td>Joke</td>
<td>85.5 (11.17)</td>
<td>2531.07 (430.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>77.0 (18.14)</td>
<td>2377.12 (480.57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous</td>
<td>Joke</td>
<td>89.0 (8.10)</td>
<td>2480.25 (356.11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>53.5 (20.15)</td>
<td>2549.48 (324.44)</td>
</tr>
<tr>
<td></td>
<td>ON</td>
<td>Unambiguous</td>
<td>Joke</td>
<td>90.0 (13.33)</td>
<td>2532.97 (387.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>78.5 (19.44)</td>
<td>2462.62 (603.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous</td>
<td>Joke</td>
<td>86.5 (8.18)</td>
<td>2600.11 (428.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>48.0 (14.38)</td>
<td>2685.21 (403.78)</td>
</tr>
</tbody>
</table>

Note: RT = response time. Values in parentheses represent standard deviation.

Data were also examined for time-out instances, in which participants failed to respond within the 5-second time limit. No participants demonstrated a considerably large number of missed responses, greater than 3 x IQR (i.e., more than 7.97% of all
responses). On average, PD patients missed 2.19% of responses, compared to 2.56% of responses for controls. However, this difference was not statistically significant ($t(18) = 0.63, p = .63$), suggesting that a response deadline of 5 seconds did not disadvantage either group.

### 3.2.1 Percentage of Correct Responses

A 2 x 2 x 2 x 2 mixed ANOVA was conducted to determine the effects of Group (control vs. PD), Medication (OFF vs. ON), Ambiguity (unambiguous vs. ambiguous), and Stimulus Type (non-joke vs. joke) on the percentage of correctly categorized stimuli. The assumption of normality was moderately violated (Glass et al., 1972); all other ANOVA assumptions were met. The ANOVA revealed a significant main effect of Stimulus Type ($F(1,18) = 17.04, p < .001, \eta^2_p = .486$), in which jokes ($M = 84.88, 95\% CI [80.22, 89.53]$) were correctly categorized more often than non-jokes ($M = 70.81, 95\% CI [66.15, 75.47]$). A significant main effect of Ambiguity was also found ($F(1,18) = 44.33, p < .001, \eta^2_p = .711$), where unambiguous stimuli ($M = 83.44, 95\% CI [79.84, 87.03]$) were categorized correctly more often than ambiguous stimuli ($M = 72.25, 95\% CI [68.66, 75.84]$). These main effects were qualified by a two-way interaction between Stimulus Type x Ambiguity $F(1,18) = 64.43, p < .001, \eta^2_p = .782$ (Figure 5). There was a simple main effect of Stimulus Type for ambiguous stimuli only ($t(26.22) = 7.25, p < .001$), in which ambiguous jokes ($M = 86.00, 95\% CI [80.82, 91.18]$) were categorized correctly more often than ambiguous non-jokes ($M = 58.50, 95\% CI [53.32, 63.68]$). Furthermore, a simple main effect of Ambiguity was found for non-joke stimuli, where ambiguous non-jokes were categorized incorrectly significantly more often than unambiguous non-jokes ($M = 83.13, 95\% CI [77.94, 88.31]$), $t(36) = -10.38, p < .001$. In other words, participants, regardless of medication status, were more likely to incorrectly categorize non-joke stimuli as having humorous intent when these stimuli contained ambiguous words.
Figure 5: Comprehension accuracy is decreased for ambiguous non-joke stimuli. Humor comprehension was evaluated as the percentage of correctly categorized joke and non-joke stimuli. Participants, regardless of group or medication status, were worse at correctly categorizing ambiguous non-jokes. Error bars represent standard error of the mean. ***\( p < .001 \)

Furthermore, a significant two-way interaction between Group x Stimulus Type emerged, \( F(1,18) = 7.68, p = .013, \eta^2_p = .299 \) (Figure 6). Simple effects analysis demonstrated that the main effect of Stimulus Type was only significant for PD patients (\( t(18) = 4.88, p < .001 \)), and was not significant for controls (\( t(18) = 0.96, p = .35 \)). In other words, PD patients correctly categorized more jokes (\( M = 87.75, 95\% \text{ CI} [81.16, 94.34] \)) than non-jokes (\( M = 64.25, 95\% \text{ CI} [57.66, 70.84] \)), but no such difference was observed in controls. Furthermore, PD patients had a significantly lower comprehension score for non-jokes compared to the control group (\( M = 77.38, 95\% \text{ CI} [70.79, 83.96] \)), regardless of medication status or stimulus ambiguity, \( t(35.64) = 2.86, p = .007 \). In other words, PD patients were more likely to erroneously categorize a non-joke stimulus as a joke than vice versa, and were also more likely to do so than controls. There were no significant three- or four-way interactions in this model.
Figure 6: Comprehension accuracy is decreased in PD patients for non-joke stimuli. Humor comprehension was evaluated as the percentage of correctly categorized joke and non-joke stimuli. PD patients were worse at successfully categorizing auditory stimuli with no humorous intent as non-jokes. Error bars represent standard error of the mean. **p < .01, ***p < .001

A follow-up exploratory analysis was performed in which we investigated whether the aforementioned Group x Stimulus Type effect would be maintained for unambiguous stimuli only, because both groups of participants had difficulty comprehending ambiguous non-joke stimuli. A 2 x 2 x 2 mixed ANOVA was conducted using humor comprehension accuracy (% correct) for unambiguous stimuli only. A significant Group x Stimulus Type interaction was indeed found, $F(1,18) = 5.41$, $p = .032$, $\eta^2_p = .231$. This was qualified by a significant simple main effect of Group for unambiguous non-joke stimuli ($t(34.55) = 2.07$, $p = .05$), in which PD patients were significantly worse at categorizing unambiguous non-jokes ($M = 77.75$, 95% CI [70.29, 85.21]) than controls ($M = 88.50$, 95% CI [81.04, 95.96]).
3.2.2 Responding Bias for Incorrect Non-Jokes

In order to clarify whether the Group x Stimulus Type interaction described above was due to reduced comprehension (i.e., inability to distinguish humorous intent) or increased humor appreciation (i.e., a tendency to find more stimuli amusing) in PD patients, we evaluated the responding bias for incorrect non-jokes. Similar to Campbell et al. (2015), we evaluated the number of non-jokes incorrectly classified in the “Joke – Funny” and “Joke – Not Funny” categories. For each participant, the difference between “Joke – Funny” and “Joke – Not Funny” responses for non-joke stimuli was normalized by dividing by the number of total incorrect non-joke stimuli. More negative values represented a bias toward decreased humor comprehension (i.e., more “Joke – Not Funny” responses) whereas more positive values represented a bias toward increased humor appreciation (i.e., more “Joke – Funny” responses). A 2 x 2 x 2 mixed ANOVA was conducted (all ANOVA assumptions were met), which yielded no significant main or interaction effects for Group, Medication, or Ambiguity. Furthermore, a one-sample t-test found that the average normalized difference value was not significantly different than 0, which suggests that our participants, regardless of group, had no systematic bias in their incorrect categorization of non-jokes. In other words, on trials where non-jokes were incorrectly categorized, participants chose the “Joke – Funny” and “Joke – Not Funny” categories at levels equal to chance.

3.2.3 Response Time (RT)

The time to make a categorization response (in msec) was also used as a measure of humor comprehension. These data were assessed for outliers above or below 3 x IQR. No extreme values were identified.

Data were entered into a 2 x 2 x 2 x 2 mixed ANOVA. All ANOVA assumptions were met. A significant main effect of Stimulus Type emerged ($F(1,18) = 7.82, p = .012, \eta^2_p = .303$) in which participants responded to non-jokes ($M = 2384.39, 95\% \text{ CI}[2213.24, 2555.53]$) more quickly than to jokes ($M = 2531.16, 95\% \text{ CI}[2360.01, 2702.31]$). A main effect of Ambiguity was also found, as participants responded more quickly to unambiguous stimuli ($M = 2405.33, 95\% \text{ CI}[2237.00, 2573.65]$) compared to ambiguous
stimuli \( (M = 2510.22, 95\% \text{ CI } [2341.89, 2678.54]) \). These main effects were qualified by an Stimulus Type x Ambiguity interaction, \( F(1,18) = 9.75, p = .006, \eta^2_p = .351 \) (Figure 7). A simple main effect of Stimulus Type was revealed for unambiguous stimuli only \( (t(35.85) = 4.19, p < .001) \), suggesting that participants were quicker in responding to unambiguous non-jokes \( (M = 2244.53, 95\% \text{ CI } [2061.81, 2427.25]) \) compared to unambiguous jokes \( (M = 2566.13, 95\% \text{ CI } [2383.41, 2748.85]) \). Furthermore, there was a simple main effect of Ambiguity for non-joke stimuli \( (t(32.68) = 4.06, p < .001) \), in which participants responded more quickly to unambiguous non-jokes compared to ambiguous non-jokes \( (M = 2524.24, 95\% \text{ CI } [2341.52, 2706.96]) \).

**Figure 7:** Participants categorized unambiguous non-jokes faster than other stimuli. Average response time (RT) in milliseconds (msec) to categorize ambiguous and unambiguous joke and non-joke stimuli. Unambiguous non-jokes were categorized significantly quicker than other stimulus types. Error bars represent standard error of the mean. ***\( p < .001 \)

A Group x Stimulus Type interaction also emerged, \( F(1,18) = 6.07, p = .024, \eta^2_p = .252 \) (Figure 8). A simple main effect of Stimulus Type for control participants was found \( (t(18) = 3.72, p = .002) \), in which controls responded to non-joke stimuli \( (M = 2250.17, 95\% \text{ CI } [2083.13, 2492.21]) \) more quickly than to joke stimuli \( (M = 2526.22, \)
95% CI [2284.18, 2768.26]). The simple main effect of Stimulus Type for PD patients was not significant, \( t(18) = -17.49, p = .82 \). There were no significant three- or four-way interactions in this model.

![Figure 8: Controls are faster at categorizing non-joke stimuli compared to joke stimuli.](image)

Figure 8: Controls are faster at categorizing non-joke stimuli compared to joke stimuli.

Average response time (RT) in milliseconds (msec) to categorize jokes and non-jokes for control and PD patient participants. Control participants were significantly quicker at making responses for non-jokes. Error bars represent standard error of the mean. ***\( p < .001 \)

3.2.4 Relationship with Clinical Measures

A multiple linear regression was conducted to determine whether disease duration, levodopa equivalent dose (LED), or freezing of gait (assessed by the N-FOG) would predict humor comprehension ability in our PD patient group. The model explained 78.92% of the variance and significantly predicted humor comprehension ability \( F(3,6) = 7.489, p = .02 \). N-FOG score contributed significantly to the model \( (B = -1.04, p = .021) \), whereas disease duration \( (B = 0.33, p = .44) \) and LED \( (B = .005, p = .53) \) did not.
3.2.5  **Relationship with Demographic and Questionnaire Measures**

Multiple linear regression was used to determine whether age, years of education, cognitive ability (MoCA), estimated premorbid IQ (AMNART), happiness (OHQ), alexithymia (TAS-20), or sense of humor (SHQ-6) would predict humor comprehension ability across all participants. The resulting model was not significant \( F(7,12) = 2.25, p = .10 \), but did account for 56.77% of the variance. SHQ score contributed significantly to the model \( B = 1.63, p = .04 \), but none of the other predictor variables demonstrated a significant contribution.

3.2.6  **Relationship with Affective Measures**

A multiple linear regression analysis was conducted to determine whether BDI-II, BAI, or SAS scores (averaged across both sessions) would predict humor comprehension ability for all participants. The resulting model was not significant \( F(3,16) = 0.90, p = .46 \), only explaining 14.4% of the variance.

3.3  **Humor Appreciation**

Average funniness ratings from the 4-point Likert-type scale response were used as a measure of humor appreciation. These data represent subjective amusement in response to each stimulus, regardless of humorous intent. These data were assessed for outliers above or below 3 x IQR. No extreme values were identified. Data are shown in Table 5.
### Table 5: Funniness ratings and reaction time (RT) by PD patients and controls.

<table>
<thead>
<tr>
<th>Group</th>
<th>Medication</th>
<th>Ambiguity</th>
<th>Stimulus Type</th>
<th>Mean Rating</th>
<th>Mean RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=10)</td>
<td>OFF</td>
<td>Unambiguous</td>
<td>Joke</td>
<td>2.24 (0.33)</td>
<td>2158.92 (572.19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous</td>
<td>Joke</td>
<td>1.09 (0.13)</td>
<td>1852.58 (452.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>1.30 (0.19)</td>
<td>1894.47 (450.11)</td>
</tr>
<tr>
<td></td>
<td>ON</td>
<td>Unambiguous</td>
<td>Joke</td>
<td>2.11 (0.51)</td>
<td>2287.78 (530.34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous</td>
<td>Joke</td>
<td>1.09 (0.09)</td>
<td>1952.02 (446.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>1.25 (0.18)</td>
<td>1863.93 (450.80)</td>
</tr>
<tr>
<td>Patient (n=10)</td>
<td>OFF</td>
<td>Unambiguous</td>
<td>Joke</td>
<td>2.12 (0.54)</td>
<td>2264.31 (430.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous</td>
<td>Joke</td>
<td>1.22 (0.27)</td>
<td>2159.43 (480.57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>1.47 (0.37)</td>
<td>2374.02 (324.44)</td>
</tr>
<tr>
<td></td>
<td>ON</td>
<td>Unambiguous</td>
<td>Joke</td>
<td>2.30 (0.50)</td>
<td>2423.38 (387.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ambiguous</td>
<td>Joke</td>
<td>1.21 (0.32)</td>
<td>2318.34 (603.84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-Joke</td>
<td>1.43 (0.32)</td>
<td>2315.13 (403.78)</td>
</tr>
</tbody>
</table>

**Note:** RT; reaction time. Values in parentheses represent standard deviation.

Data were also examined for time-out instances, in which participants failed to respond within the 5-second time limit. Once again, there were no participants identified who demonstrated a considerable number of missed trials, above 3 x IQR (i.e., more than 6.09% of all responses). On average, PD patients missed 1.56% of responses, compared to 1.44% of responses for controls. This difference was not significant ($t(18) = -0.15, p = .88$), suggesting that a response deadline of 5 seconds did not disadvantage either group.

#### 3.3.1 Funniness Rating

A 2 x 2 x 2 x 2 mixed ANOVA was conducted to investigate the effects of Group (control vs. PD), Medication (OFF vs. ON), Ambiguity (unambiguous vs. ambiguous), and Stimulus Type (non-joke vs. joke) on funniness ratings. The assumption or normality was moderately violated (Glass et al., 1972); all other ANOVA assumptions were met. The ANOVA revealed a significant main effect of Stimulus Type, $F(1,18) = 165.30, p < .001$, $\eta^2_p = .902$. Jokes ($M = 2.21, 95\% \text{ CI} [2.06, 2.36]$) were rated as more funny than non-jokes ($M = 1.26, 95\% \text{ CI} [1.11, 1.41]$), confirming that across participant groups and medication state, and regardless of whether the stimuli were ambiguous or not, our humorous stimuli indeed elicited humor appreciation responses. A significant main effect
of Ambiguity was also found ($F(1,18) = 15.13, p < .001, \eta^2_p = .457$), in which ambiguous stimuli were rated funnier ($M = 1.79, 95\% \text{ CI } [1.66, 1.93]$) than unambiguous stimuli ($M = 1.67, 95\% \text{ CI } [1.54, 1.81]$). However, a significant two-way interaction was found between Stimulus Type x Ambiguity ($F(1,18) = 9.87, p = .006, \eta^2_p = .354$), suggesting that the main effect of Ambiguity only held for non-joke stimuli (Figure 9). Specifically, ambiguous non-jokes ($M = 1.37, 95\% \text{ CI } [1.21, 1.52]$) were rated significantly funnier than unambiguous non-jokes ($M = 1.15, 95\% \text{ CI } [1.00, 1.31]$), $t(35.97) = 4.98, p < .001$.

Figure 9: Ambiguous non-jokes rated funnier than unambiguous non-jokes.
Humor appreciation was measured as the average funniness rating on a 4-point Likert-type scale (1 = not funny at all, 2 = mildly funny, 3 = moderately funny, 4 = extremely funny). Across stimuli, jokes were rated significantly more funny than non-jokes. Furthermore, ambiguous non-joke stimuli were rated by participants, regardless of medication status, to be funnier than unambiguous non-joke stimuli. Error bars represent standard error of the mean. ***$p < .001$

A significant two-way interaction between Group x Medication was found, $F(1,18) = 5.06, p = .037, \eta^2_p = .219$. However, this was qualified by a significant three-way Group x Medication x Stimulus Type interaction, $F(1,18) = 4.58, p = .046, \eta^2_p = .203$ (Figure 10). The simple interaction effect of Group x Medication was significant for jokes ($F(1,18) = 8.72, p = .009, \eta^2_p = .326$), but not for non-jokes. This suggests that the effect
of levodopa on the appreciation of humorous jokes was different for each group. A follow-up analysis evaluated the effect of Medication for each Group, but only for jokes. This revealed a significant simple main effect of Medication for controls ($t(18) = 2.55, p = .02$), but not for PD patients ($t(18) = -1.63, p = .12$). Specifically, controls ON medication had significantly lower humor appreciation ratings ($M = 2.13, 95\% \text{ CI } [1.86, 2.41]$) compared to controls OFF medication ($M = 2.27, 95\% \text{ CI } [1.99, 2.54]$). Altogether, this suggests that levodopa medication suppressed the appreciation of joke stimuli in control participants. No other significant three- or four-way interactions were found in the model.

![Figure 10](image)

**Figure 10: Controls ON levodopa experience decreased humor appreciation for jokes.**
Humor appreciation was measured as the average funniness rating on a 4-point Likert-type scale (1 = not funny at all, 2 = mildly funny, 3 = moderately funny, 4 = extremely funny). Control participants demonstrated decreased humor appreciation while ON levodopa, but only for joke stimuli. Error bars represent standard error of the mean. *$p < .05$*

### 3.3.2 Responding Bias for Correct Jokes

Humor appreciation was also evaluated as the number of correctly identified jokes categorized as “Funny” compared to correct jokes categorized as “Not Funny”. Again, the
difference between “Funny” jokes and “Not Funny” jokes was normalized by dividing by the total number of correctly categorized jokes. More positive values reflect a bias toward choosing the “Funny” category, whereas more negative values reflect a bias toward the “Not Funny” category. A 2 x 2 x 2 mixed ANOVA was conducted to determine the effects of Group (control vs. PD), Medication (OFF vs. ON), or Ambiguity (unambiguous vs. ambiguous) on these bias scores. The assumption or normality was moderately violated (Glass et al., 1972); all other ANOVA assumptions were met. The ANOVA revealed a main effect of Ambiguity, $F(1,18) = 10.19, p = .005, \eta^2_p = .362$. Participants across groups and medication state demonstrated a bias toward categorizing ambiguous jokes as “Funny” ($M = 0.51, 95\% \text{ CI } [0.33, 0.70]$) more often than unambiguous jokes ($M = 0.37, 95\% \text{ CI } [0.18, 0.56]$).

3.3.3 Response Time (RT)

Participants’ average time to make a funniness rating response (in msec) was also examined. These data were assessed for outliers above or below 3 x IQR. No extreme values were identified.

A 2 x 2 x 2 x 2 mixed ANOVA was conducted to examine the effects of Group (PD vs. control), Medication (ON vs. OFF), Ambiguity (ambiguous vs. unambiguous), and Stimulus Type (joke vs. non-joke) on funniness rating RT. The assumption or normality was moderately violated (Glass et al., 1972); all other ANOVA assumptions were met. We found a significant main effect of Stimulus Type ($F(1,18) = 14.10, p = .001, \eta^2_p = .439$), in which non-jokes ($M = 2091.24, 95\% \text{ CI } [1922.98, 2259.50]$) were rated significantly faster than jokes ($M = 2250.98, 95\% \text{ CI } [2082.72, 2419.24]$). This was qualified by a significant Group x Stimulus Type interaction, $F(1,18) = 5.70, p = .028, \eta^2_p = .241$ (Figure 11). The simple main effect of Stimulus Type was only significant for control participants ($t(18) = 4.34, p < .001$), but not for PD patients ($t(18) = -58.14, p = .35$). Specifically, control participants were much quicker to rate non-joke stimuli ($M = 1890.75, 95\% \text{ CI } [1652.80, 2128.70]$) compared to joke stimuli ($M = 2152.09, 95\% \text{ CI } [1914.13, 2390.04]$). In addition, a simple main effect of Group emerged for non-joke stimuli ($t(20.66) = -2.48, p = .022$), suggesting that control participants rated non-joke stimuli more quickly than PD patients ($M = 2291.73, 95\% \text{ CI } [2053.78, 2529.68]$).
Figure 11: Controls were quicker to give funniness ratings for non-joke stimuli.
Average response time (RT) in milliseconds (msec) to rate the funniness of joke and non-joke stimuli for control and PD patient participants. Control participants were significantly quicker at rating non-joke stimuli compared to joke stimuli, and were also quicker to rate non-jokes stimuli than PD patients. Error bars represent standard error of the mean. *p < .05, ***p < .001

Furthermore, a significant Ambiguity x Stimulus Type interaction emerged, $F(1,18) = 4.57, p = .047, \eta^2_p = .202$ (Figure 12). A significant simple main effect of Stimulus Type was found for both unambiguous ($t(29.06) = 4.32, p < .001$) and ambiguous stimuli ($t(29.06) = 2.16, p = .04$), although the strength of this effect differed.
**Figure 12: Non-jokes rated more quickly for both unambiguous and ambiguous stimuli.**

Average response time (RT) in milliseconds (msec) to rate the funniness of joke and non-joke stimuli for control and PD patient participants. Non-jokes were rated more quickly than jokes, but the strength of this relationship differed for unambiguous and ambiguous stimuli. Error bars represent standard error of the mean. *p < .05, ***p < .001

A significant Group x Ambiguity interaction was also found, $F(1,18) = 4.47$, $p = .049$, $\eta^2_p = .199$ (Figure 13). A significant simple main effect of Group for ambiguous stimuli was found ($t(19.66) = -2.32$, $p = .031$), in which control participants ($M = 1980.01$, 95% CI [1744.46, 2215.57]) were quicker to provide funniness ratings for ambiguous stimuli compared to PD patients ($M = 2350.24$, 95% CI [2114.68, 2585.79]), $t(19.66) = -2.32$, $p = .03$.
Figure 13: Controls were quicker to make funniness ratings for ambiguous stimuli compared to PD patients.
Average response time (RT) in milliseconds (msec) to rate the funniness of joke and non-joke stimuli for control and PD patient participants. Control participants were significantly quicker at rating ambiguous stimuli compared to PD patients. Error bars represent standard error of the mean. *p < .05

3.3.4 Relationship with Clinical Measures

Multiple linear regression was used to determine whether disease duration, levodopa equivalent dose (LED), or freezing of gait (assessed by the N-FOG) would predict humor appreciation in our PD patient group. The model was unable to significantly predict humor appreciation responses, $F(3,6) = 2.88, p = .13$, but did account for a large proportion of the variance ($r^2 = .59$).

3.3.5 Relationship with Demographic and Questionnaire Measures

A multiple linear regression was conducted to determine whether age, years of education, cognitive ability (MoCA), estimated premorbid IQ (AMNART), happiness (OHQ), alexithymia (TAS-20), or sense of humor (SHQ-6) would predict funniness ratings across all participants. The resulting model was marginally significant ($F(7,12) =$
2.52, \( p = .07 \) and accounted for 59.53% of the variance. MoCA (\( B = -0.08, p = .04 \)) and SHQ-6 scores (\( B = -0.08, p = .008 \)) were significant predictors of funniness rating.

3.3.6  **Relationship with Affective Measures**

Finally, a multiple linear regression was conducted to determine whether depression (BDI-II), anxiety (BAI), or apathy (SAS) could predict humor appreciation for all participants. The resulting model was not significant (\( F(3,16) = 1.32, p = .30 \)) and only accounted for 19.87% of the variance.
Chapter 4

4 Discussion

The present study represents, to our knowledge, the first investigation of verbal humor comprehension and appreciation in PD. PD patients and age-matched healthy controls completed a humor processing task that distinguished between humor comprehension (i.e., ability to identify humorous intent) and humor appreciation (i.e., subjective amusement in response to humorous stimuli) while ON and OFF levodopa medication. We aimed to determine whether PD patients experienced deficits in humor comprehension, particularly while OFF levodopa, compared to controls, and whether levodopa medication would have a negative effect on humor appreciation in both groups. In brief, we found that PD patients demonstrated reduced humor comprehension for non-jokes, that is, they more often erroneously identified humorous intent when none was actually present. We also found that control participants found jokes less funny while ON levodopa medication. Taken together, these results suggest that PD patients have deficits in DS-mediated humor comprehension and that VS-mediated humor appreciation is vulnerable to dopamine overdose via levodopa in healthy elderly controls. This study represents an important first step in identifying humor processing deficits related to PD, and provides a foundation for future studies to further investigate these effects.

4.1 Demographic, clinical, and questionnaire measures

A significant difference was identified between PD and control groups for OHQ scores (Table 1). Specifically, controls had higher OHQ scores than PD patients, indicating greater life happiness. However, this group difference did not appear to have a meaningful influence on the results of the present study, as there was no significant relationship between OHQ scores with any of our outcome measures.

Interestingly, there was no significant group difference in sense of humor (Table 1), despite previous evidence suggesting that PD patients have a decreased sense of humor compared to controls (Thaler et al., 2012). However, we did observe a trend in which PD patients had lower SHQ-6 scores ($M = 18.6$) than controls ($M = 20.8$), with a
large effect size (Cohen’s $d = 0.92$). Future, well-powered studies should aim to replicate this effect.

### 4.1.1 Higher depression, anxiety, and apathy in PD patients

PD patients demonstrated significantly higher levels of depression, measured with the BDI-II, than control participants (Table 2). This was not an unexpected finding, as depression affects nearly one-quarter of PD patients (Goodarzi et al., 2016). However, the average BDI-II score for PD patients was 11.7, which is below the recommended cut-off score of 13 for mild depression (Beck et al., 1996). Therefore, although our PD patient sample was significantly more depressed than our control group, they did not demonstrate clinically significant levels of depression. Although several previous studies have established a relationship between depression and the use of particular humor styles (e.g., Ibarra-Rovillard & Kuiper, 2011; Rnic et al., 2016), there is currently little evidence available as to whether depression affects humor comprehension or appreciation. To our knowledge, the only study investigating a possible relationship between humor comprehension and depression was conducted by Uekermann et al. (2008). The authors demonstrated that patients diagnosed with major depression perform worse than healthy controls on a humor comprehension task in which they were asked to choose the appropriate punch line ending for a given joke set-up. The patient group also rated the correct and slapstick punch line endings as less humorous than the control group. These data suggest that major depression could lead to deficits in humor comprehension and reduced humor appreciation. However, it is not known whether these results could extend to those with milder (i.e., subclinical) depression.

Our PD patient group also demonstrated significantly greater anxiety than healthy controls, as measured with the BAI (Table 2). Again, this was not unexpected, as anxiety reportedly affects approximately one-third of PD patients (Mele et al., 2018). The average BAI score for PD patients was 9.4, which falls within the lower range of mild anxiety (i.e., 8-15), but below the cut-off of 16 for clinical anxiety (Beck et al., 1988). Similar to depression, the relationship between anxiety and humor comprehension and appreciation has received relatively little attention. Doris and Fierman (1956) found that participants with high levels of anxiety tend to approve less of cartoons depicting aggressive humor.
than participants with low anxiety. The groups did not differ in their understanding of the
cartoons, indicating that anxiety might affect humor appreciation, but not comprehension.
Schick et al. (1972) also found that participants with high anxiety tended to give higher
funniness ratings to familiar “Peanuts” comic strips and lower ratings to unfamiliar comic
strips with novel characters, compared to controls with low anxiety. Taken together, these
data suggest that anxiety’s effect on humor appreciation might depend on the style of
humor, as well as the individual’s previous exposure to a humorous stimulus.

Finally, our PD patients reported greater apathy, measured with the SAS, both
while ON medication compared to OFF medication and compared to our control group
(Table 2). PD patients ON medication had an average SAS score of 16.9, which meets the
cut-off of ≥ 14 for clinical apathy (Starkstein et al., 1992). PD patients also met this cut-off
while OFF medication, with an average SAS score of 14.1. This was not an
unexpected finding, as apathy is present in approximately one-third of PD patients (Mele
et al., 2019). Apathy is only recently being recognized as its own distinct condition,
separate from other disorders such as depression (Kirsch-Darrow et al., 2011; Levy et al.,
1998; Marin, 1991). There is currently no research on whether apathy affects humor
comprehension or appreciation. However, apathy has been shown to negatively affect
various cognitive abilities in the elderly, including attention, processing speed, verbal
fluency, and memory (Montoya-Murillo et al., 2019), and has been associated with worse
cognitive function and greater risk for dementia in PD (Dujardin et al., 2009; Varanese et
al., 2011).

4.2 Humor Comprehension

4.2.1 PD patients erroneously categorize non-jokes as jokes

For humor comprehension (i.e., percentage of jokes and non-jokes correctly
categorized as such), PD patients demonstrated significantly worse categorization
accuracy for non-jokes compared to jokes, as well as compared to controls’ non-joke
performance (Figure 6). In other words, PD patients incorrectly categorized non-jokes as
having humorous intent when none was actually present. Interestingly, non-joke
comprehension deficits have also been found in other studies. For example, Samson and
Hegenloh (2010) had individuals with Asperger syndrome indicate whether or not they understood the humorous component of various cartoon jokes and non-joke control stimuli. Surprisingly, these participants sometimes indicated that they understood the humor in the non-joke control pictures. The authors suggest that this could have been due to a social desirability bias induced by participants’ knowledge and awareness that they were taking part in a humor processing study. This could partially explain our findings that PD patients had more non-joke errors. Specifically, PD patients might have been more likely to categorize stimuli that they could not comprehend as jokes either a) because they were expecting to hear jokes in the study, or b) wanted to appear as though they had a sense of humor, which is a socially desirable trait. If the stimulus in question was actually a joke, this would be marked as a correct response and falsely inflate the participant’s joke comprehension score. However, if the stimulus was actually a non-joke, their socially desirable response would decrease their comprehension score for non-jokes. That this could have happened in the present study is plausible and supported by a nonsignificant trend for PD patients to have higher comprehension accuracy for jokes compared to controls.

In a similar study by Chau (2010), participants with right frontal pole and OFC lesions were asked to indicate whether or not they understood auditory jokes and puns. The lesion group made more false-positive responses, that is, they were more likely than controls to indicate that they understood non-jokes. Chau (2010) contends that these patients must have a reduced threshold for joke detection as a result of their lesions, and that the right PFC might play a role in determining what constitutes a joke. PD patients with left-side symptom onset (i.e., greater right hemisphere degeneration) have been reported to have worse cognitive symptom severity compared to those with right-side symptom onset (Bentin et al., 1981; Holtgraves et al., 2010; Tomer et al., 1993). Therefore, it is possible that PD patients with left-side symptom onset could show a reduced threshold for joke detection, similar to patients with RHD. In the present study, only 4 of our PD patients had left-side symptom onset, which prevented us from conducting statistical analyses with sufficient power to draw conclusions regarding the effect of side of symptom onset. Future research with larger sample sizes able to stratify PD patients by affected side could investigate whether humor comprehension deficits are
specific to left-side symptom onset. However, laterality of symptom onset in PD does not necessarily equate to clean hemispheric lesions, and therefore might not affect humor comprehension in such a drastic way as RHD.

Finally, Campbell et al. (2015) also found that when evaluating joke and non-joke cartoons, healthy participants made more classification errors for non-jokes. In order to clarify whether this was due to reduced humor comprehension or increased humor appreciation, Campbell et al. (2015) evaluated the median number of incorrect non-joke responses that were categorized as funny jokes or unfunny jokes. They found that of the non-jokes that were misclassified, more tended to be categorized as unfunny jokes, and took this to reflect humor comprehension errors rather than increased humor appreciation responses.

Similar to Campbell et al. (2015), we investigated whether participants had a responding bias for non-joke errors. Instead of comparing median responses, we used normalized difference scores to determine participants’ tendency to incorrectly categorize a non-joke as either a funny joke or an unfunny joke. No differences were found between groups or medication status, and there was no difference in responding bias between ambiguous and unambiguous non-joke errors. Participants in both groups seemed to make these non-joke categorization errors at random. This reveals an important limitation to the trichotomous response methodology proposed by Campbell et al. (2015) that was used in the present study. Although using three response options (“Joke – Funny”, “Joke – Not Funny”, and “Not a joke”) allows us to distinguish between humor comprehension and appreciation, the chances of participants choosing a “joke” response is inherently inflated. If a participant responded completely at random, they would be twice as likely to choose one of the two joke categories over the non-joke category. Because we used an equal number of joke and non-joke stimuli, a participant responding completely at random would therefore get more joke stimuli correct and more non-joke stimuli incorrect. For this reason, and due to the lack of responding bias toward the “Joke – Funny” category for non-joke errors, we interpret the increased number of non-joke errors in our PD group to reflect reduced humor comprehension, rather than increased humor appreciation.
PD patients’ deficit in humor comprehension for non-jokes did not seem to be worse for stimuli containing ambiguous words (i.e., puns), as originally predicted. Instead, both groups demonstrated worse humor comprehension for ambiguous non-jokes (Figure 5). In other words, non-jokes containing ambiguous words (i.e., double meanings) were often erroneously thought to contain humorous intent when none was actually present. Recalling that puns simultaneously invoke both meanings of an ambiguous word, this could represent a flaw in our methodology in which ambiguous non-jokes failed to provide enough context for participants to settle on a single meaning of the ambiguous word. However, our exploratory analysis of humor comprehension using only unambiguous stimuli found that the Group x Stimulus Type interaction remained significant, and that PD patients remained worse at categorizing unambiguous non-jokes compared to controls. It is also possible that we have identified an effect of aging on the processing of ambiguous jokes and non-jokes, and that due to our small sample size, we were underpowered to tease out any additional effect of PD on the processing of ambiguous stimuli. Indeed, age has been shown to affect humor comprehension abilities (Greengross, 2013; Mak & Carpenter, 2007; Schaier & Cicirelli, 1976; Shammi & Stuss, 2003). Future research could investigate how aging and PD independently affect ambiguous joke/non-joke processing by including young healthy controls in a similar study.

4.2.2 Controls respond faster to non-jokes compared to jokes, but PD patients do not

Analysis of humor comprehension RT revealed that control participants made categorization responses more quickly for non-jokes compared to jokes (Figure 8). This finding is corroborated by other studies that have also found an effect of faster RT for non-joke stimuli. For example, Mobbs et al. (2003) found that healthy participants were quicker to respond as to whether they found a cartoon stimulus funny or not funny when that stimulus was non-humorous. Goel and Dolan (2001) found similar results for verbal joke stimuli. Vaid et al. (2003) investigated the time-course of humor comprehension by measuring participants’ RTs to words that were semantically related to the initial interpretation of a joke, or to the true joke meaning. Participants demonstrated greater priming (i.e., shorter RTs) to the initial interpretation word after only hearing the set-up
of the joke. During the incongruity detection phase of the joke, there was a sudden priming of an additional, humorous interpretation. From this, it can be inferred that participants might respond quicker to non-jokes because they do not require the activation and interpretation of a secondary meaning of the stimulus. This is corroborated by our finding that across participants, unambiguous non-jokes, in particular were categorized more quickly than other stimulus types (Figure 7). This is the only type of stimulus that does not require any re-interpretation, and thus would lead to quicker RTs overall.

However, not all studies have reported RT facilitation for non-jokes. For example, Samson et al. (2008) found that participants were quicker to respond whether they found a cartoon funny or not funny when the stimulus was a pun, compared to a non-joke baseline. In fact, the non-joke baseline had the longest average RT. However, these non-joke baselines contained “irresolvable incongruity”, which could have required participants to make more attempts at resolving the incongruity before accepting that the stimulus was a non-joke, thus taking longer to make their response. Other studies have also found that participants are quicker to respond to jokes compared to non-jokes (Bartolo et al., 2006; Cunningham & Derks, 2005).

Although control participants revealed the expected pattern, categorizing non-joke faster than joke stimuli (Mobbs et al., 2003), PD patients showed no RT advantage for non-jokes relative to jokes. That is, interestingly, our PD patient group had nearly identical mean RTs for joke and non-joke stimuli. It is unlikely that this is the result of motor difficulties (e.g., bradykinesia), as the PD group did not demonstrate significantly slower responses for joke stimuli compared to controls, and there were no significant ON-OFF effects on RTs for joke or non-joke stimuli for PD patients. Although bradykinesia is a cardinal feature of PD, our results are not entirely surprising as PD patients frequently demonstrate similar response latencies in the ON and OFF states, and/or relative to control participants when simple oral or manual responses (e.g., button presses or reaches toward a target) are required (e.g., Merritt et al., 2017; X. Q. Yang et al., 2018), as was the case in the present study.

However, PD patients’ lack of an expected facilitation in RTs for non-joke compared to joke stimuli could provide further evidence of humor comprehension
difficulties in PD, mirroring our accuracy findings wherein PD patients categorized non-joke stimuli more poorly than controls and less correctly than they categorized joke stimuli. Non-joke stimuli have a singular meaning; even those that contain ambiguous words require the listener to settle on a singular interpretation of the content (Bekinschtein et al., 2011). This has been offered to account for the latency advantage for non-jokes relative to jokes (Vaid et al., 2003). We speculate that PD patients might have had more difficulty activating or selecting the appropriate meaning for non-jokes. This is corroborated by our finding that PD patients had significantly reduced non-joke accuracy. Indeed, studies have shown that PD patients demonstrate delayed spreading activation during lexical processing tasks (Angwin et al., 2009; Arnott et al., 2001), which might suggest that these patients have difficulty accessing appropriate and alternate meanings of a stimulus. In other words, PD patients in the present study might have had more trouble accessing the intended interpretation of non-joke stimuli, which could have contributed to relatively longer RTs than expected, in line with the more error-prone categorization. However, as this notion is based on non-significant results, it must be confirmed in future, well-powered studies.

4.2.3 Implications for a humor comprehension deficit in PD

In the present study, PD patients demonstrated a humor comprehension deficit for verbal humor, which took the form of reduced accuracy in identifying instances where humor was not actually present. Medication status (ON or OFF levodopa) did not affect PD patients’ humor comprehension performance, and comprehension was no worse for pun stimuli (i.e., ambiguous jokes), contrary to what was originally predicted. Furthermore, PD patients demonstrated a lack of RT facilitation for non-joke stimuli though controls showed the expected RT advantage for non-joke stimuli. We interpret this pattern of latencies in PD patients as further evidence of a humor comprehension deficit. These data also suggest that the humor comprehension deficit observed here might reflect difficulty activating or selecting an appropriate and alternate meanings for verbal stimuli, causing patients to fail to identify non-humorous interpretations for non-joke stimuli.
Degeneration of the SNc and subsequent DS dysfunction seems to cause reductions in information processing speed and working memory (Cooper et al., 1994; Gabrieli et al., 1996; Jokinen et al., 2013; S. J. G. Lewis et al., 2005; Revonsuo et al., 1993), which has been directly related to language comprehension deficits in PD (Grossman, 1999; Lee et al., 2003; McKinlay et al., 2009; Monetta et al., 2008; Monetta & Pell, 2007). Specifically, PD patients experience difficulties comprehending complex sentences, particularly in the OFF medication state (Grossman et al., 2001; Johari et al., 2019; Papagno et al., 2013). The present study identified a deficit for non-joke comprehension in PD patients. This could be related to more general sentence comprehension deficits, but does not explain why PD patients were able to comprehend humorous stimuli, which are arguably more linguistically complex than the non-joke stimuli.

Furthermore, PET studies have demonstrated that PD patients’ language comprehension deficit is associated with reduced activity in the ACC and left frontal cortex, which are normally activated in healthy controls during sentence processing (Grossman et al., 1992, 1993). fMRI studies have also showed that PD patients have significantly less activity in the left caudate, left MFG, and right posterolateral temporal cortex during complex sentence comprehension (Grossman et al., 2003; Ye et al., 2012). These areas overlap with those involved in humor processing (Martin & Ford, 2018), suggesting that PD patients’ deficits in complex sentence processing might implicate a deficit in verbal humor comprehension. Neuroimaging studies in PD patients during humor processing are needed to clarify these precise mechanisms.

PD patients also demonstrate delays in semantic activation resulting in deficits in ambiguity processing, which is especially pronounced while OFF medication (Angwin et al., 2009; Papagno et al., 2013; Pederzolli et al., 2008). In the present study, we did not find support for our original prediction that PD patients would show increased comprehension deficits for puns compared to non-puns. However, studies that have stratified PD patients into separate groups with and without mild cognitive impairment (MCI) have found that only the group with MCI experienced difficulty processing sentences with ambiguities (Berg et al., 2003; F. M. Lewis et al., 1998). Unfortunately,
stratifying our PD patients into high and low cognitive ability groups is not possible with the current sample size. Future research should investigate whether deficits in pun comprehension exist in PD, and whether this is related to cognitive decline.

4.3 Humor Appreciation

4.3.1 Controls experience reduced humor appreciation ON levodopa, but PD patients do not

PD causes progressive degeneration of dopaminergic neurons in the SNc, followed by the VTA in later stages of the disease. In early PD, when the VTA is relatively intact, levodopa medication can induce deficits in functions mediated by VTA-innervated regions, such as the VS (i.e., dopamine overdose hypothesis; Figure 2). For example, reward-based learning is decreased in healthy young and elderly participants, as well as early-stage PD patients ON, but not OFF levodopa medication (Hiebert et al., 2019; Hiebert, Seergobin, Vo, Ganjavi, & MacDonald, 2014; Vo et al., 2016, 2018).

Although humor comprehension, covered previously, has been shown to implicate DS and cortical networks reciprocally connected to SNc-innervated DS (Campbell et al., 2015), humor appreciation implicates the VS, VTA, and other VTA-innervated brain regions such as the amygdala (Mobbs et al., 2003). Due to this reliance on disparate brain regions that are unequally dopamine-deprived in PD, different patterns of performance were expected for humor comprehension and appreciation in PD, in healthy elderly controls, and related to exogenous dopamine therapy. In the present study, we found that control participants rated joke stimuli as significantly less funny while ON levodopa medication compared to OFF medication (Figure 10). This partially confirms our original hypothesis that across groups, humor appreciation would be reduced ON medication due to the dopamine overdose hypothesis.

Previous studies have indeed documented cognitive deficits in healthy participants during administration of levodopa. For example, healthy young adults given levodopa are impaired in probabilistic reversal learning (Vo et al., 2016) and stimulus-response learning (Vo et al., 2017), presumably due to overdose of the VS, which plays a key role in reward-based learning. Although older healthy adults do experience age-related
declines in striatal dopamine (Bäckman et al., 2000; Wang et al., 1998), this levodopa-induced impairment has been found to persist in older healthy adults for VS-mediated functions. For example, despite the fact that their baseline probabilistic reversal learning performance is reduced compared to young healthy adults, older adults indeed experience learning impairments while ON levodopa (Vo et al., 2018). Levodopa also impairs facial emotion perception in healthy older adults, accompanied by decreased activation in the VTA-innervated amygdala (Delaveau et al., 2005, 2007). These seemingly VS-specific functional deficits following levodopa administration likely emerge in healthy older adults is because age-induced dopamine decline appears to affect SNc/DS functions to a greater extent than VTA/VS functions. This notion is supported by studies demonstrating that levodopa actually improves motor cortex function (Kishore et al., 2014) and memory (Coulthard et al., 2019) in healthy older adults. This could explain why VS-mediated humor appreciation was reduced by levodopa in healthy elderly controls in the present study, whereas DS-mediated humor comprehension was not affected.

No significant difference in humor appreciation across medication status was found for PD patients. Although we originally predicted that levodopa would reduce humor appreciation for both groups, it is possible that our PD patient group was further progressed in the disease than expected and beginning to experience VTA degeneration and subsequent VS dysfunction. Indeed, PD patients with a disease duration greater than 5 years have been shown not to experience levodopa-induced deficits in probabilistic reversal learning (A. A. MacDonald et al., 2013). This is presumably because levodopa medication would restore, rather than overdose, dopamine in the degenerated VTA/VS in late-stage PD patients. In the present study, three PD patients had disease durations greater than 5 years, and two patients had disease durations of 4 years, meaning that later-staged patients accounted for a significant proportion of our patient sample. Statistical comparisons between PD patients with short and long disease durations are not feasible with the present sample size, but there was indeed a non-significant trend for PD patients to rate jokes as funnier while ON medication (Figure 10). Our small sample, and the significant proportion of patients with more advanced disease stage, raise the possibility that some of our patients have sufficient VTA degeneration that they might not experience dopamine overdose. Unfortunately, our small sample precludes exploring this
hypothesis empirically. We are contemplating future studies in which patients are intentionally stratified by disease duration and severity, to further investigate this supposition.

4.3.2 **Ambiguous stimuli rated as funnier than unambiguous stimuli**

Our analysis of humor appreciation ratings also revealed that ambiguous non-jokes were rated by participants to be funnier than unambiguous non-jokes (Figure 9). This reflects our findings for humor comprehension, in which participants made more categorization errors for ambiguous non-jokes than for unambiguous non-jokes. It is therefore likely that some of our ambiguous non-joke stimuli were erroneously thought to contain humorous content, and that these were also interpreted as subjectively funnier.

We also analyzed participants’ responding bias for correctly categorized jokes and found that ambiguous jokes tended to be categorized as funny jokes (rather than unfunny jokes) more often than unambiguous jokes. Taken together, this suggests that ambiguous stimuli overall were more humorous to participants than unambiguous stimuli. Interestingly, this effect was not found in a previous study from which we drew the majority of our stimuli (Bekinschtein et al., 2011). This discrepancy could be due to our expansion of the stimulus set, or due to the different populations that were investigated (i.e., PD patients and healthy elderly in the current study compared to healthy young adults in Bekinschtein et al.’s study). Indeed, several studies have demonstrated that healthy elderly participants tend to have greater humor appreciation than younger participants (Greengross, 2013; Schaier & Cicirelli, 1976).

4.3.3 **Controls rate non-jokes faster than jokes, but PD patients do not**

Similar to our findings for humor comprehension RT, control participants also made funniness ratings for non-joke stimuli more quickly than for joke stimuli (Figure 11). Once again, this finding is corroborated by studies that have found faster RT to non-joke stimuli (Goel & Dolan, 2001; Mobbs et al., 2003) and by our finding that non-joke stimuli were rated more quickly for both ambiguous and unambiguous stimuli (Figure 12). This could be because participants gave low funniness ratings to non-joke stimuli (M
and likely did not have to deliberate over the degree of subjective amusement they experienced in response to non-jokes.

There was no significant difference in humor appreciation RT for jokes compared to non-jokes in the PD patient group. Once again, it is unlikely that this is a result of bradykinesia, as there was no significant difference between PD patients and controls for joke rating RT. Instead, we believe that for non-jokes, PD patients had more difficulty settling on a particular humor rating because they were impaired in the comprehension of non-joke stimuli in the first place. In other words, if PD patients experienced difficulty while determining that a non-joke stimulus did not contain humorous intent, they might have additional difficulty providing a subjective amusement rating for that stimulus, and thus take longer to make the response.

4.4 Limitations

There are several important limitations to the present study. First, a sample size of 20 participants across groups is admittedly small and is also below our target sample size of at least 34. For some of our analyses, particularly the regressions investigating relationships between our humor processing measures and the demographic, clinical, and questionnaire data obtained, this small sample size might have compromised statistical power to a large degree, leading to Type II errors. PD is an extremely heterogeneous disease in which a variety of clinical phenotypes might present. Therefore, studies with larger samples of PD patients are better able to capture this clinical heterogeneity and produce more generalizable results. A larger sample size would have allowed us to stratify our results by degree of cognitive ability, side of symptom onset, and disease duration for PD patients, which could have clarified our results. Future research into humor processing in PD should aim to replicate and expand upon the results of this study with larger samples of clinically well-characterized PD patients, permitting the exploration of the impact of clinical features, PD subtypes, severity and duration of PD, as well as treatments on elements of humor processing. Furthermore, our measures of PD severity were limited to disease duration, LED, and N-FOG scores. However, the use of MDS-UPDRS scores would likely be a more sensitive measure of disease severity and
could provide greater insight into the relationship between PD severity and aspects of humor processing.

Another limitation of this study is that participants were aware of the fact that they were taking part in an experiment investigating humor processing and that they would be hearing humorous audio clips. As noted by Samson and Hegenloh (2010), participants with awareness about the study’s purpose might be inclined to produce socially desirable responses. This could have created a bias toward categorizing audio clips as jokes, particularly if the participant was experiencing difficulties with humor comprehension and was unsure of which category to choose. Future studies could therefore attempt to conceal the true purpose of the study. For example, the study could be framed as an investigation of language processing, rather than humor processing.

Another important methodological limitation that might have falsely inflated joke comprehension accuracy is that the trichotomous response profile provides twice the number of categories for jokes compared to non-jokes. If participants were responding completely at random, they would choose one of the “joke” categories twice as often as the “non-joke” category. Although this response profile is an improvement over previous humor processing studies in that it allows for participants to distinguish between their comprehension and appreciation of a stimulus, the methodology could be improved upon to equalize the probability of choosing “joke” and “non-joke”. The simplest solution would be to add a fourth response option for stimuli that participants believe to be non-jokes, but find funny (i.e., “Non-joke – Funny”). Alternatively, participants could be asked directly about the speaker’s intentions regarding the stimuli (e.g., “Did the speaker intend to be humorous?”), which would result in Yes/No responses that would still capture humor comprehension separate from appreciation. This could be followed by a funniness rating response (as done in the present study) to capture humor appreciation toward a particular stimulus, regardless of participants’ response to the initial comprehension question.

The present study investigated humor processing using auditory verbal joke and non-joke stimuli. However, humor comes in many different forms (e.g., cartoon, slapstick, nonsense), and therefore our results are limited solely to discussions about
verbal humor. Furthermore, our use of traditional verbal joke stimuli limits the ecological validity of the study, because these jokes are rarely encountered in everyday life. Future studies could explore the processing of other forms of humor in PD. Our use of both ambiguous (i.e., puns) and unambiguous joke stimuli along with corresponding non-joke stimuli does provide a more in-depth investigation into the specific components of verbal humor processing in PD. However, there are indications that the stimuli could be improved to reduce confounds. For example, item analyses should be conducted with larger sample sizes to refine the stimuli set, in order to identify potential non-jokes that are commonly mistaken for jokes, which could then be removed and replaced with a more appropriate non-joke stimulus.

Finally, this study represents a primarily behavioral account of humor processing in PD. Although we can make inferences about the brain regions involved through our knowledge of PD and dopamine pathways, we cannot conclusively determine which brain regions might be implicated in potential humor processing deficits in PD with the present data. Therefore, future investigations should include a neuroimaging component in order to elucidate regional brain activity differences that arise during humor processing in PD. Neuroimaging might also clarify the role of the cortex in PD-related humor processing deficits.

4.5 Conclusions

The current investigation of humor processing in PD represents an important step in evaluating the disease’s social symptoms. Humor is a uniquely human phenomenon with a well-documented role in social interaction, therefore any potential deficits in humor comprehension and appreciation could have a negative impact on patients’ daily lives. From a basic science perspective, the results of this study also shed light on the role of dopamine and the involvement of particular brain regions (e.g., DS, VS) in the distinct processes of humor comprehension and appreciation.

We found that PD patients were deficient in their ability to correctly identify non-joke stimuli (i.e., no humorous intent). Overall, we interpret this to reflect a more general deficit in humor comprehension as methodological limitations might have falsely inflated
PD patients’ humor comprehension accuracy scores for joke stimuli. There was no evidence that PD patients’ humor comprehension abilities were affected by dopaminergic medication, or that patients were particularly deficient in the comprehension of puns. Future research should corroborate this with different humor processing tasks and neuroimaging results to provide converging evidence for a DS-mediated humor comprehension deficit in PD. Furthermore, we found that levodopa decreased humor appreciation for jokes in healthy elderly controls, providing support for the dopamine overdose hypothesis and evidence that the VS mediates subjective amusement in response to humorous stimuli. No effects of levodopa on humor comprehension and appreciation in PD were noted, somewhat at odds with our predictions. We surmise that this arose due to a quite varied PD sample in the current study. Our small sample size prevented us from investigating the impact of clinical variables (e.g., disease severity, disease duration, cognitive impairment, side of symptom onset) that might interact with elements of humor processing. Further, we were not able to remove or mitigate variance related to the clinical heterogeneity of our sample because of the small sample size. In sufficiently-powered future studies, we plan to investigate humor comprehension and appreciation, ON and OFF levodopa, in PD patients with short and long disease durations, a range of disease severity, as well as in different clinical phenotypes, symptoms, and therapeutic regimens. Contrasting performance of thoroughly, clinically-characterized PD patients to healthy older and younger controls who are treated with exogenous dopamine will provide further context for understanding humor processing in PD, a topic about which very little is known.
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Appendices

Appendix A: Letter of Information and Consent Form

LETTER OF INFORMATION AND CONSENT FORM

In this consent document, “you” always refers to the study participant. If you are a substitute decision maker (SDM) (i.e. someone who makes the decision of participation on behalf of a participant), please remember that “you” refers to the study patient. If an SDM is needed for this study, you will be asked to review and sign this consent form on behalf of the participant.

Study Title
Distinguishing the roles of ventral and dorsal striatum in cognition

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Sponsoring Agency
The research is funded by a Canada Excellence Research Chair to Dr. Adrian Owen, an Academic Medical Association of Southwestern Ontario Opportunity Fund and Natural Sciences and Engineering Research Council of Canada awarded to Dr. Penny MacDonald.

Purpose
You are being asked to participate in a research project designed to help us understand more about attention, memory, and how people make every day decisions. The study will help show which parts of the brain are involved in these functions. It will also help us to understand whether certain illnesses that affect the brain such as strokes or Parkinson’s disease, or obsessive-compulsive disorder change the way people pay attention, remember, and make decisions. Understanding these changes might help us to provide better care for these patients ultimately. We will aim to recruit approximately 200 patients with Parkinson’s disease, 200 healthy volunteers, matched in age to PD patients, 200 patients with strokes, 200 patients with neurological or psychiatric disorders that might implicate the striatum (a brain region of interest), and 200 healthy volunteers. The criteria to participate in this study were previously outlined in the recruitment letter that you were given.

Procedures
If you agree, you will be asked to one or two testing sessions at the Brain and Mind Institute or the Robarts Research Institute at the University of Western Ontario. Each session is expected to last approximately 1.5 hours, but may go as long as 3 hours. The first session will begin with a short clinical interview to evaluate your general health. Your heart rate and blood pressure might also be recorded. A screening neurological examination will be performed. You will also be asked to complete a few standard questionnaires to assess aspects of your mood and temperament. In each session, you will next perform a computerized test that is aimed at testing basic aspects of thinking, memory, or problem solving. Explanations of the paper and pencil tests will be provided orally and detailed written instructions will be given prior to the computerized test on each day. You will have the chance to ask questions and will be encouraged to do so before beginning the tests. Practice trials will also be provided so that you will be comfortable with the computerized test and so that you understand thoroughly what you’re asked to do.

Your permission is also requested for Dr. MacDonald to review any CT or MRI scans of the brain that you have previously undergone. This will help us better understand the results of the testing.

Experiments involving functional magnetic resonance imaging

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During testing, you might perform tests on a computer that are aimed at testing basic aspects of thinking, memory, or problem solving while you are in a magnetic resonance imaging (MRI) machine. With MRI, we are able to measure blood flow non-invasively in various parts of your brain as a marker of brain activity while you perform specific thinking functions. We will also collect images of your brain in the MRI to measure different brain structures.

Patients with Parkinson’s disease
If you are a patient with Parkinson’s disease, you will be tested twice, once while you are taking your Parkinson’s medication and once after you have abstained from taking your Parkinson’s medication for at least 12 hours on two separate days.

Healthy control participants or patients with neurological (e.g. stroke, epilepsy, multiple sclerosis, multiple systems atrophy, progressive supranuclear palsy, cortico-basal-ganglionic degeneration, Lewy body dementia, ataxia, Huntington’s disease, Alzheimer’s disease), as well as sleep disorders (e.g. rapid eye movement sleep behavioural disorder or RBD, restless leg disorder and obstructive sleep apnea), or psychiatric disorder (e.g. obsessive-compulsive disorder) other than Parkinson’s disease
If you are a non-patient volunteer or a patient with a neurological or psychiatric disorder other than Parkinson’s disease, you might perform the tasks once or twice. In all testing sessions, you will take all of your regularly prescribed medications. In some studies, you might also take dopaminergic therapy or a placebo (i.e., cornstarch) in one session or across two sessions.

Patients with addiction (e.g. alcohol, opioids, marijuana)
You will be asked to abstain from all illicit substances as well as alcohol for a minimum of 48 hours prior to testing. Upon arrival on your testing date, you will complete an OraSure Oral Fluid (Saliva) Drug Test and an Alco-Screen Oral Fluid (Saliva) Alcohol Test to confirm compliance with these instructions. In all testing sessions, you will take all of your regularly prescribed medications. In some studies, you might also take dopaminergic therapy or a placebo (i.e., cornstarch) in one session or across two sessions.

Healthy control participants studied while taking dopaminergic therapy
For non-patient volunteers, in some experiments you will perform tasks once while taking a dose of Levocarb or Pramipexole, common medications that are used to treat Parkinson’s disease, and once while taking an inactive or placebo substance (i.e., cornstarch). The order in which you receive these substances will be randomly determined across participants. You will not be informed of the substance that you are given in either testing session and the experimenter will also be blind to which substance you are given on a particular day. This is done to reduce any effects of expectation that might be induced by knowing that you are receiving active treatment. Levocarb contains 100 mg of levodopa (L-3,4-dihydroxyphenylalanine) and 25 mg of carbidopa. Levodopa is transformed in the brain into...
dopamine whereas pramipexole mimics dopamine. Dopamine is a neurotransmitter produced naturally in the brain that is involved in regulating movement and some aspects of thinking and memory. Carbidopa is a substance that does not cross into the brain but is given to stop the levodopa from being converted to dopamine before it reaches the brain. Carbidopa reduces side effects that can occur due to dopamine being produced in the body rather than in the brain, such as nausea or lowering of blood pressure.

**Experiments involving propranolol or atenolol**
You might be asked to perform some tasks once while taking a dose of propranolol or atenolol, and once while taking an inactive or placebo substance (i.e., cornstarch). The order in which you receive these substances will be randomly determined across participants. You will not be informed of the substance that you are given in either testing session and the experimenter will also be blind to which substance you are given on a particular day. This is done to reduce any effects of expectation that might be induced by knowing that you are receiving active treatment. Propranolol and atenolol are beta blockers. Beta blockers compete with the same receptors as adrenaline, slowing the sympathetic nervous system to lower heart rate and blood pressure.

**Experiments involving polysomnographic sleep recordings**
You might be asked to undergo polysomnographic sleep recordings during either a 3-h daytime nap or 8-h overnight session. Polysomnography (PSG) is a non-invasive technique that uses surface electrodes applied to the scalp and face to measure brain activity during different sleep-wake cycles.

**Experiments involving robotic arm manipulation**
We will ask you to perform a motor learning task. This will take approximately 40 minutes. You will be asked to grasp the handle of one or two robot arms, and point to visual targets displayed on a virtual-reality display. You will be asked to point to targets one after another. Depending on the phase of the experiment, the robot may be programmed to apply small forces (a few grams) to your hand during movement. The robot will measure the movement of the handle (e.g., when movement starts, how fast it is, how curved the trajectory of movement is as you move to the targets) as an index of motor learning. Throughout the experiment, your muscle activity will be measured with surface electromyography (EMG) by small, non-invasive electrodes placed on top of the skin with adhesive tape. These electrodes will be placed on the upper chest, just below the collarbone. If you have chest hair, the areas where surface recording will take place might need to be shaved in order to collect good quality data. You are welcome to remove it yourself before arriving to the study, or we can provide razors and shaving cream before we attach the electrodes.

**Experiments involving electroencephalography**

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You might be asked to undergo electroencephalography (EEG) recordings during either the experimental session. EEG is a non-invasive technique that uses surface electrodes applied to the scalp and face to measure brain activity during rest or during performance of various cognitive tasks.

**Experiments involving audiometric assessment**
You may be asked to listen to sounds through headphones and report when you detect the sound and when you can no longer hear the sound. This part is expected to take no longer than 12 minutes.

**Experiments involving beat/rhythm discrimination**
You may be asked to complete auditory tasks involving discrimination of auditory sequences, and/or tapping during or after listening to auditory sequences. For these tasks, auditory sequences will be presented via headphones at a comfortable intensity level. Tapping will be performed on a computer keyboard or external device (e.g., a drum pad) capable of recording tapping information.

**Experiments involving affective processing**
You might be asked to view pictures and/or sounds that portray either neural content (e.g., chairs, glasses) or negatively valenced content, some of which is graphic or disturbing in nature (e.g., guns, threat/attack, body mutilation), or a series of faces. Your psychophysiological responses to these stimuli will be monitored at all times during the task using electromyography (EMG), galvanic skin response (GSR), electrocardiography (ECG), heart rate, blood pressure, and respiration.

**Experiments involving virtual reality**
You might be asked to interact in real-world situations using a virtual reality head set. During the test, your movements will be tracked using cameras. The virtual reality head set creates a virtual environment that you can see and interact with.

**Experiments involving driving simulation**
You may be asked to perform driving tasks using a driving simulator. During the test you will be sitting in a cockpit designed to replicate a driver's seat and surrounded by large screens. Tests will involve performing driving tasks (i.e. navigation, turning, etc...).

**Experiments involving social processing**
You might be asked to view a series of faces and make judgments about them (e.g., emotion, age), and/or listen to a variety of jokes while evaluating how funny they were. Throughout these activities, your facial expression activity will be continuously recorded with electromyography (EMG).

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Benefits
Your participation in this study is of no direct benefit to you.

Risks
If you require treatment for any injuries or illness directly related to procedures implemented during the study, or if you suffer side effects while on study medication, you should contact your study doctor as soon as possible. The necessary medical care will be provided to you at no additional cost to you. You do not waive any legal rights by signing the consent form.

Participants performing computerized tasks
There are no known physical risks associated with performing computerized tasks. You may find some of the tasks dull or tiring.

Experiments involving functional magnetic resonance imaging
The Food & Drug Administration (USA) has indicated that for clinical diagnosis an ‘insignificant’ risk is associated with human MRI exposure at the intensities used in this project. Current Canadian guidelines follow the USA guidelines. Although very rare, injury and deaths have occurred in MRI units from unsecured metal objects being drawn at high speeds into the magnet or from internal body metal fragments of which the subject was unaware or had not informed MRI staff. To minimize this latter possibility it is essential that you complete a screening questionnaire. Other remote but potential risks involve tissue burns and temporary hearing loss from the loud noise inside the magnet. The latter can be avoided with ear headphone protection that also allows continuous communication between the subject and staff during the study.

This MRI machine uses a strong magnet and radio waves to make images of the body interior. You will be asked to lie on a long narrow couch for an hour while the machine gathers data. During this time you will be exposed to magnetic fields and radio waves. You will not feel either. You will, however, hear repetitive tapping noises that arise from the magnets that surround you. You will be provided with earplugs or headphones that you will be required to wear to minimize the sound and protect your hearing. The space within the large magnet in which you lie is somewhat confined, although we have taken many steps to relieve the “claustrophobic” feeling. There are no known significant risks with this procedure at this time because the radio waves and magnetic fields, at the strengths used, are thought to be without harm. The exception is if you have a cardiac pacemaker, or a metallic clip in your body (e.g., an aneurysm clip in your brain), have severe heart disease, body piercings, tattoos containing metallic ink or slow release pharmaceutical skin patches.

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There is a possibility that you will experience a localized twitching sensation due to the magnetic field changes during the scan. This is not unexpected and should not be painful. However, you can stop the exam at anytime. The magnetism and radio waves do not cause harmful effects at the levels used in the MRI machine. However, because the MR scanner uses a very strong magnet that will attract metal, all metallic objects must be removed from your person before you approach the scanner. In addition, watches and credit cards should also be removed as these could be damaged (these items will be watched for you).

For experiments involving electrophysiological recording (e.g., EMG) inside of the MRI; while rare, incidents of tissue burning have been reported due to the recording electrodes and cables heating up inside of the magnet. However, this risk is largely eliminated when proper equipment and procedures are used. The surface electrodes and cables we use have been specially designed for use within the MRI and there have been no known burn incidents reported with this particular equipment. Furthermore, you will also be separated from the cables by an insulating barrier, and your skin will be prepared according to recommended safety procedures prior to electrode placement.

Patients with Parkinson’s disease
For Parkinson’s patients who are tested off of their Parkinson’s medications, you likely will experience an increase in your Parkinson’s symptoms. If you do not return to your usual level of function after resuming your medication at the conclusion of the testing session, you are invited to contact Dr. MacDonald to discuss your concerns as well as medication strategies for getting back to your usual self.

Participants taking dopaminergic therapy
If you are a non-patient volunteer taking levodopa or pramipexole, there is a potential risk of developing side effects following drug administration. More serious side effects reported are based on chronic use of these medications in patients, and are not expected to develop in this study given the single, low-dose of drug administered. Less serious side effects are largely peripheral effects (e.g., nausea) and should be minimized through co-administration of Carbidopa. Any side effects that do occur are temporary and should quickly subside. In the unlikely situation that your symptoms persist, you are invited to contact the experimenter to discuss your concerns.

Less serious side effects include: mild nausea, dry mouth, loss of appetite; heartburn, diarrhea, constipation; headache, dizziness, drowsiness, blurred vision; sneezing, stuffy nose, cough, other cold symptoms; sleep problems (insomnia), strange dreams, muscle pain, numbness/tingly feelings, skin rash/itching. More serious side effects include: severe allergic reactions; restless muscle movements in your eyes, tongue, jaw, or neck; worsening of tremors (uncontrolled shaking); high fever, stiff muscles, sweating, fast or uneven heartbeats, difficulty
breathing, feeling like you might pass out; seizure (convulsions); painful or difficult urination; severe nausea, vomiting, or diarrhea; uneven heart rate or fluttering in your chest; confusion, hallucinations, anxiety, agitation, depressed mood, thoughts of suicide or hurting yourself; unusual or intense urges (e.g., gambling, sexual urges); chest pain or heavy feeling, pain spreading to the arm or shoulder.

Experiments involving propranolol
You should not take propranolol if you have asthma. If you are a volunteer taking propranolol, there is a potential risk of developing side effects following drug administration. More serious side effects reported are based on chronic use of these medications in patients, and are not expected to develop in this study given the single, low-dose of drug administered. Any side effects that do occur are temporary and should quickly subside. In the unlikely situation that your symptoms persist, you are invited to contact the experimenter to discuss your concerns.

Less serious side effects include: fatigue; nausea, vomiting, diarrhea, constipation, stomach cramps; decreased sex drive, impotence, of difficulty having an orgasm; trouble concentrating, sleep problems (insomnia). More serious side effects include: severe allergic reactions; fast, slow, or uneven heartbeats; feeling light-headed or fainting; feeling short of breath even with mild exertion; dilated neck veins, swelling of ankles or feet; nausea, upper stomach pain, itching, loss of appetite, dark urine, clay-coloured stools, jaundice (yellowing of skin or eyes); cool pale skin; cold feeling in hands or feet; depression, confusion, hallucinations, slurred speech, headache; seizures; severe skin reaction (blistering or peeling skin)

Experiments involving polysomnographic sleep recording and electroencephalography
The only potential risk is for individuals with extremely sensitive skin. These individuals may have a slight skin irritation where the skin has been gently exfoliated during electrode application. When we apply the electrodes to the surface of the skin, we use a gentle, hypoallergenic medical-grade exfoliant, called NuPrep, to clean the skin where the electrodes will be placed. Any mild irritation to the skin normally lasts less than a few hours.

Experiments involving robotic arm manipulation
The principal potential risk is injury caused by the robotic arm. However, injury is very unlikely and we have implemented a range of safety precautions that are widely used for the prevention of injury in studies of human motor control involving robots. A number of safety precautions have been implemented with respect to the robot linkage. In addition to minimizing the applied force, we test for forces at the endpoint. If forces exceed 10 N all forces are immediately set to zero. Additional vendor supplied algorithms limit the workspace over which forces may be applied. Moreover, all experimental protocols were tested in full prior to the experiment. Both you and the experimenter have a switch that instantaneously deactivates the robot. In studies over the past 20 years using this setup at both Western and McGill we

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have not had a single injury or adverse event. The KINARM End-Point Lab is frequently used in clinical populations with movement related disorders, and is marketed as an assessment tool in these populations.

Experiments involving affective processing
There is the possibility of emotional and/or mental distress resulting from viewing images with extremely graphic, violent, frightening, disturbing, and/or emotionally distressing content and listening to sounds that portray equally upsetting or distressing emotional content. There is also a small possibility that some of the recording electrodes may produce mild skin irritation.

Experiments involving virtual reality
Virtual reality can be disorienting and cause dizziness. The only potential risk is for individuals to develop nausea and vomiting during the task. Before any testing begins, you will undergo a period of acclimatization involving slow movements and interactions in the virtual environment to ensure you are comfortable with performing the task.

Experiments involving driving simulation
Much like virtual reality, the driving simulator can also be disorienting that may lead to nausea and vomiting. Before any testing begins, you will undergo a period of acclimatization involving slow movements and interactions in the virtual environment to ensure you are comfortable with performing the task.

Confidentiality
The investigators will maintain all information collected in this study strictly confidential, shared only with individuals directly involved in this study, except as may be required by court order or by law. To further ensure your confidentiality, information collected from you will be devoid of any unique personal identifier and will be filed under an anonymous subject number. If any publication or presentation results from this research, you will not be referred to by name and no potentially identifying information will be released. The information collected in the course of this study is kept on file in a secure location for no less than 25 years. If you decide you do not want this information to be kept on file, simply advise the research team of your wishes, and your record will be destroyed.

Your contact and demographic information collected for this study, will be stored in a secure, password-protected database held at Western University. Only the researchers of this study and the BrainsCAN coordinator, who administers the database system, will have access to your identifiable information (e.g. name, date of birth, diagnoses, etc.). The BrainsCAN coordinator will not need to review any of your information unless you have consented to be a part of the OurBrainsCAN registry. If you agree to be a part of the OurBrainsCAN registry and have indicated
that the researchers of this study can enter your identifiable information, they will include the contact and demographic information collected for this study.

If you would like to be contacted about future research studies for which you (or your child) may be eligible, you can choose to have your identifiable information entered into “OurBrainsCAN: University of Western Ontario’s Cognitive Neuroscience Research Registry” by the researchers of this study OR alternatively you can be given the web address of OurBrainsCAN where you are able to enter your (or your child’s) information. This is a secure database of potential participants for research at Western University, which aims to enrol 50,000 volunteers over a period of 5 years. The information in this database will be stored indefinitely. The records are used only for the purpose of recruiting research participants and will not be released to any third party. When you are invited to participate future research studies, you will be given a full description of what your involvement would entail. You are, of course, free to turn down any invitation. If, at any time, you decide that you do not want your (your child’s) contact information to be a part of this database, please contact [Contact Information] to remove your information.

Consent to Use and Disclose Information for Research Subjects
Representatives of the University of Western Ontario Health Sciences Research Ethics Board might be granted direct access to your medical records. A representative of the University of Western Ontario Health Sciences Research Ethics Board might contact you or might require access to your study-related records to monitor the conduct of the research. Similarly, as this study is affiliated with Lawson Research, Lawson’s quality assurance and education may access the study data for quality assurance purposes. By signing the consent, you also permit the principal investigator to use and disclose health information about yourself for the purposes of this study.

Incidental Findings
The tests you undergo in this study are not intended to diagnose or monitor any medical conditions you may have. Nevertheless, if information that might be relevant to your care is discovered incidentally, this information will be communicated to you, and at your request, to your physician.

Compensation
You will receive $20-50 depending on the length (1.5hrs vs. 3hrs) and type (behavioural only vs. behavioural with an MRI component) of study in which you are taking part. This is to compensate you for the time and inconvenience associated with your participation. You will also be reimbursed for parking costs.
Voluntary Participation/Withdrawal from the Study
Your participation in this research is completely voluntary. You may refuse to continue performing the tasks in this study at any time without any consequences. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care. You do not waive any of your legal rights by signing the consent form. If the research investigators find it necessary, and/or in your best interest, you will be asked to withdraw from the study. In the event that you withdraw from the study for any reason, you will receive compensation for the sessions that you attended, even if you did not complete the entire session. Your cost of parking will also be reimbursed.

Contact Information
If you have any questions or concerns regarding the study, you may contact the principle investigator. If you wish to speak to a neutral individual who is not involved in the study at all and who will answer any questions about your rights as a research participant or about the conduct of the study, you may contact a Patient Relations Specialist from London Health Sciences Centre at [redacted]

Results
If you’re interested in obtaining the results of the study, we will gladly provide you with a summary of our findings once the research is complete. Please let the investigator know if you would like a summary of the results mailed or emailed to you.
Consent Form

Distinguishing the roles of ventral and dorsal striatum in cognition

Principle Investigator: Penny A. MacDonald, MD, PhD

I (__________________________) have read the Letter of Information and Consent form and have had the nature of the study explained to me and I agree to participate. All questions have been answered to my satisfaction. I have been provided a copy of the Recruitment/Information Letters and the Consent form. I freely and voluntarily consent to participate in this study.

______________________________  ____________________________
Signature of participant          Date

Your signature on this form indicates that you are acting as a substitute decision maker(s) for the participant and the study has been explained to you and all your questions have been answered to your satisfaction. You agree to allow the person you represent to take part in the study. You know that the person you represent can leave the study any time.

______________________________  ____________________________
Signature of substitute decision maker (if applicable)  Relationship to Participant  Date

______________________________  ____________________________
Signature of investigator          Date

I have discussed this clinical research study with the participant using a language that is understandable and appropriate. I believe that I have fully informed this participant of the purpose, duration etc. of this research study and its possible benefits and risks and I believe the participant understood this explanation.

______________________________  ____________________________
Signature of person assisting in consent process  Date

12/13

Version: 29/August/2019
Consent Form

initials: ________
Optional Consent to be Added to OurBrainsCAN Recruitment Database

I consent to being added to the OurBrainsCAN: University of Western Ontario’s Cognitive Neuroscience Research Registry to be contacted about future research studies for which I (or my child) may be eligible:

Please initial:

_______ Yes, I already signed-up.

_______ Yes, the researcher can enter my information into the database on my behalf.

_______ Yes, please provide me the link to join the database myself.

Participant’s Name (Please print): ________________________________

Participant’s Signature: ________________________________

Date: ________________________________
Appendix B: Ethics Approval

Date: 27 November 2019
Tec: Dr. Penny MacDonald
Project ID: 102018

Study Title: Distinguishing the roles of ventral and dorsal striatum in cognition (REB #18517)
Application Type: Continuing Ethics Review (CER) Form
Review Type: Delegated
REB Meeting Date: 03/Dec/2019
Date Approval Issued: 27/Nov/2019
REB Approval Expiry Date: 29/Nov/2020

Dear Dr. Penny MacDonald,

The Western University Research Ethics Board has reviewed the application. This study, including all currently approved documents, has been re-approved until the expiry date noted above.

REB members involved in the research project do not participate in the review, discussion or decision.

Western University REB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2), the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The REB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 0000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Daniel Wyrczynski, Research Ethics Coordinator, on behalf of Dr. Joseph Gilbert, IHSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).
Appendix C: Health & Demographics Questionnaire

For administrator’s use only

<table>
<thead>
<tr>
<th>Date (dd/mm/yy):</th>
<th>Session #:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject #:</td>
<td>Group:</td>
</tr>
<tr>
<td></td>
<td>Time:</td>
</tr>
</tbody>
</table>

Health and Demographic Questionnaire

Please print and fill out this form as accurately as possible and bring it with you to your first appointment session. If you are attending your appointment with another participant, please ensure you both have your own personal copies filled out.

1. Basic Demographic Information

Date of Birth: ________________ Age: _____
Weight: ______ Height: ______
Handedness: __________ Gender: ______
First language: ______________ Other languages: __________________
Level of Education and total years (e.g. 4 years high school, 4 years university, etc.)

____________________________
Occupation: __________________

2. Health-Related Information

A. Smoking History (please circle): Never Smoker Ex-Smoker Current Smoker
If current smoker, indicate how many years and how many cig/day: ________________
If ex-smoker, indicate year that you quit; how many years smoking; how many cig/day:

____________________________

B. Alcohol History
Average number of drinks per week: __________
Has there ever been heavy alcohol consumption? (please circle) Yes No
If yes, when, for how long, and estimate your weekly alcohol consumption during that time:

____________________________

C. Other Drug History
Have you ever taken street drugs or other drugs that were not prescribed by a physician (please circle)? Yes No
If yes, when, what drugs, how frequently and over what period of time?
D. Eye Glasses (only if applicable)

What is the prescription of your eye glasses? __________

Without the aid of glasses are you able to see near objects well (please circle)? Yes No

Without the aid of glasses are you able to see far objects well (please circle)? Yes No

E. Obsessive-compulsive disorder (OCD; only if applicable)

What year were you diagnosed with OCD? ________________

Are you currently taking medication to treat your OCD? ________________

If yes, what medication? ________________

F. Parkinson’s Disease (PD; only if applicable)

What year were you diagnosed with Parkinson’s disease? ________________

Which side of the body is more affected? ________________

3. Previous Medical Problems

Have you had any major health problems or do you have any chronic, ongoing medical conditions such as high blood pressure, high cholesterol, diabetes, thyroid problems, multiple sclerosis or epilepsy? Have you had any strokes, heart attacks/ heart surgeries, significant head trauma, or cancer? If you’ve had cancer, what kind and what treatments did you receive (e.g. chemotherapy)? Have you ever had more than one seizure? Answer in the space below.
4. Family Medical Problems

Is there anyone in your family with a neurological or serious psychiatric illness such as PD, Huntington's, epilepsy, strokes at a young age (< 50 for men and < 60 for women)? Is there anyone who had trouble walking or with balance, needing a wheelchair or a walker at a young age? Any family members with dementia (such as Alzheimer's), schizophrenia, bipolar/manic depression, or severe depression or anxiety requiring hospitalization or close follow up by a psychiatrist? Answer in the space below.
5. Current Medication

Please list any medications you are currently taking, what they are treating for specifically, and the prescribed dosage.
Appendix D: Levodopa Safety Screening Questionnaire

Levodopa FAQ

What does the experiment involve?
You will complete one session on l-dopa and the other session on placebo. You will not be made aware of which substance you will be taking for either session. To ensure maximal drug absorption, you will be asked to abstain from caffeine, alcohol, and smoking the day before and morning of testing. You will also be asked to limit yourself to light meals on the day of testing.

What are you trying to find?
The study for which you are being recruited is designed to help us understand more about attention, memory, and how people make everyday decisions. We are also interested in the effects of l-dopa therapy on these cognitive abilities. A more thorough explanation of our hypotheses and predictions will be disclosed to you upon the completion of the experiment.

What is l-DOPA?
Dopamine is a neurotransmitter chemical produced endogenously in the brain that is involved in movement regulation and aspects of cognition. Levodopa (L-3,4-dihydroxyphenylalanine) is a dopamine precursor that is converted to dopamine through dopa-decarboxylase upon crossing the blood brain barrier. We will use a single dose of a clinically available agent, which contains 100 mg of levodopa and 25 mg of carbidopa. Carbidopa is a decarboxylase inhibitor that cannot cross the blood brain barrier, and therefore stops the early conversion of levodopa to dopamine at the peripheral level (i.e., outside the brain). Both drug and placebo will be double blind administered in identical capsules orally in a randomized, double-blind, crossover procedure. The placebo used will be a standard placebo substance (i.e., corn starch). This strategy not only provides a corresponding control for patients tested in the ON session, it also will provide additional support for the effects of dopaminergic medication from PD studies. Pharmacological manipulation protocols using levodopa have previously been used safely in healthy individuals (Delaveau et al., 2007, Delaveau et al., 2009, Onur et al., 2011). Testing will begin 1 hour after drug ingestion to allow time for drug absorption and to achieve peak plasma dopamine levels.

Are there side effects to l-DOPA?
There is a potential risk of developing side effects following drug administration. More serious side effects reported are based on chronic use of levodopa in patients with Parkinson’s disease, and are not expected to develop in this study given the single, low-dose of drug administered. Less serious side effects are largely peripheral effects (e.g., nausea) and should be minimized through co-administration of Carbidopa. Any side effects that do occur are temporary and should quickly subside. In the unlikely situation that your symptoms persist, you are invited to contact the experimenter to discuss your concerns. Serious side effects may occur if you present with contraindications for l-dopa (e.g., taking a specific medication, have a history of certain healthy issues, etc.). It is important that you complete the screening questionnaire as accurately as possible to ensure your eligibility and safety in this experiment.
Screening Questionnaire

*Please answer the following questions as accurately as possible. Your responses will be reviewed by the experimenter prior to your participation.*

<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are you NOT between the ages of 18-80?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you have a history of overusing alcohol, prescription, or illegal drugs?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you currently take any prescription medications?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Are you currently taking tetrabenazine or monoamine oxidase (MAO) inhibitors?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Have you been diagnosed with any form of dementia?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Are you currently taking medications for problems with thinking or memory such as:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Donepezil (Aricept)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rivastigmine (Exelon)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Galantamine (Reninyl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Memantine (Exila)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Methylphenidate (Ritalin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you have any personal history of a neurological condition (e.g., stroke, multiple sclerosis, seizures)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Are you currently significantly depressed or anxious enough to need treatment from a psychiatrist?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Have you ever experienced hallucinations or paranoid thinking?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Do you have a medical history of any of the following:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Bleeding disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Breathing problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serious eye problems (e.g., wide-angle glaucoma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Heart or blood vessel problems (e.g., arrhythmias, heart attack, angina)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Kidney disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Peptic ulcer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Are you currently pregnant, suspect you are pregnant, or attempting to conceive?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Are you currently breastfeeding?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Do you have any other serious health issues or concerns?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Have you participated in a levodopa study previously?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix E: Epworth Sleepiness Scale (ESS)

For administrator's use only

Date (dd/mm/yy):

Subject #:

Session #:

Time:

Group:

Score:

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the situations described below, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:-

0 = would never doze
1 = Slight chance of dozing
2 = Moderate chance of dozing
3 = High chance of dozing

<table>
<thead>
<tr>
<th>Situation</th>
<th>Chance of dozing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting and reading</td>
<td></td>
</tr>
<tr>
<td>Watching TV</td>
<td></td>
</tr>
<tr>
<td>Sitting, inactive in a public place (e.g. a theatre or a meeting)</td>
<td></td>
</tr>
<tr>
<td>As a passenger in a car for an hour without a break</td>
<td></td>
</tr>
<tr>
<td>Lying down to rest in the afternoon when circumstances permit</td>
<td></td>
</tr>
<tr>
<td>Sitting and talking to someone</td>
<td></td>
</tr>
<tr>
<td>Sitting quietly after a lunch without alcohol</td>
<td></td>
</tr>
<tr>
<td>In a car, while stopped for a few minutes in the traffic</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

Score:

0-10 Normal range
10-12 Borderline
12-24 Abnormal
Appendix F: Barratt Impulsiveness Scale (BIS)

For administrator’s use only

Date (dd/mm/yy):

Score:

Sub-scores: A: CI: M: P: SC: CC:

Barratt Impulsiveness Scale (BIS-11)

**Directions:** People differ in the ways they act and think in different situations. This is a test to measure some of the ways in which you act and think. Read each statement and put an X on the appropriate circle on the right side of this page. **Do not** spend too much time on any statement. Answer quickly and honestly.

<table>
<thead>
<tr>
<th></th>
<th>Rarely/Never</th>
<th>Occasionally</th>
<th>Often</th>
<th>Almost Always/Always</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I plan tasks carefully.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>I do things without thinking.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>I make-up my mind quickly.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>I am happy-go-lucky.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>I don’t “pay attention.”</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>I have “racing” thoughts.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>I plan trips well ahead of time.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>I am self-controlled.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>I concentrate easily.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>I save regularly.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>I “squirm” at plays or lectures.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>I am a careful thinker.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>I plan for job security.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>I say things without thinking.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>I like to think about complex problems.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>I change jobs.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>I act “on impulse.”</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>I get easily bored when solving thought problems.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>I act on the spur of the moment.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>I am a steady thinker.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>I change residences.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>I buy things on impulse.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>I can only think about one thing at a time.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>I change hobbies.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>I spend or charge more than I earn.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>I often have extraneous thoughts when thinking.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>I am more interested in the present than the future.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>I am restless at the theatre or lectures.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>I like puzzles.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>I am future oriented.</td>
<td>1 2 3 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Appendix G: Bond & Lader Visual Analogue Mood Scale (BL-VAS)

<table>
<thead>
<tr>
<th>For administrator’s use only</th>
<th>Date (dd/mm/yy):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject #:</td>
<td>Session #:</td>
</tr>
<tr>
<td>Score:</td>
<td>Medication:</td>
</tr>
<tr>
<td>Time:</td>
<td></td>
</tr>
</tbody>
</table>

### Bond & Lader Visual Analogue Mood Scale

**Instructions:** For each line below, put a vertical mark at the point that represents how you feel at this moment. Ensure to draw your line all the way through the horizontal line. The ends of each scale are to present the “most” that you have ever felt in your life.

- **ALERT** —— “DROWSY” mm
- **CALM** —— “EXCITED” mm
- **STRONG** —— “FEEBLE” mm
- **MUZZY** —— “CLEAR HEADED” mm
- **WELL** —— “CLUMSY” mm
- **COORDINATED** ——
- **LETHARGIC** —— “ENERGETIC” mm
- **CONTENTED** —— “DISCONTENTED” mm
- **TROUBLED** —— “TRANQUIL” mm
- **MENTALLY SLOW** —— “QUICK WITTED” mm
- **TENSE** —— “RELAXED” mm
- **ATTENTIVE** —— “DREAMY” mm
- **CONTENTED** —— “PROFICIENT” mm
- **HAPPY** —— “SAD” mm
- **ANTAGONISTIC** —— “FRIENDLY” mm
- **INTERESTED** —— “BORED” mm
- **WITHDRAWN** —— “SOCIABLE” mm
Appendix H: Montreal Cognitive Assessment (MoCA)

**Montreal Cognitive Assessment (MOCA)**
Version 7.1 Original Version

**VISUOSPATIAL / EXECUTIVE**
1. **Copy Cube**
   - Points: \( \frac{3}{5} \)
2. **Draw CLOCK (Ten past eleven)**
   - Points: \( \frac{3}{5} \)

**NAMING**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhino</td>
<td>( \frac{1}{3} )</td>
</tr>
<tr>
<td>Camel</td>
<td>( \frac{1}{3} )</td>
</tr>
</tbody>
</table>

**MEMORY**
- Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

<table>
<thead>
<tr>
<th>Trial</th>
<th>FACE</th>
<th>VELVET</th>
<th>CHURCH</th>
<th>DAISY</th>
<th>RED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ATTENTION**
- Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order.
  - Points: \( \frac{2}{2} \)

<table>
<thead>
<tr>
<th>List</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBACMNAAJKLBAFADDEAAJAMOFAAB</td>
<td>( \frac{1}{1} )</td>
</tr>
</tbody>
</table>

- Read list of letters. The subject must tap with his hand at each letter. No points if \( \geq 2 \) errors.

<table>
<thead>
<tr>
<th>Serial 7 subtraction starting at 100</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>93, 86, 79, 72, 65</td>
<td>( \frac{3}{3} )</td>
</tr>
</tbody>
</table>

**LANGUAGE**
- Repeat: I only know that John is the one to help today.
- The cat always hid under the couch when dogs were in the room.

**ABSTRACTION**
- Similarity between e.g. banana - orange – fruit.
- Train – bicycle.
- Watch – ruler.

**DELAYED RECALL**
- Has to recall words with no cue.

<table>
<thead>
<tr>
<th>Category cue</th>
<th>Points for UNCUED recall only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \frac{5}{5} )</td>
</tr>
</tbody>
</table>

**ORIENTATION**
- Date: \( \frac{1}{6} \)
- Month: \( \frac{1}{6} \)
- Year: \( \frac{1}{6} \)
- Day: \( \frac{1}{6} \)
- Place: \( \frac{1}{6} \)
- City: \( \frac{1}{6} \)

Administered by: ____________________________

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Normal: \( \frac{26}{30} \)

Add 1 pt if \( \leq 12 \) yr. edu

TOTAL: \( \frac{1}{30} \)
Appendix I: American version of Nelson Adult Reading Test (AMNART)

**AMNART - Participant Form**

1. ache  
2. debt  
3. pint  
4. depot  
5. chord  
6. bouquet  
7. deny  
8. capon  
9. heir  
10. aisle  
11. subtle  
12. nausea  
13. gauge  
14. naïve  
15. thyme  
16. courteous  
17. algae  
18. fetal  
19. quadruped  
20. epitome  
21. superfluous  
22. chamois  
23. papyrus  
24. asthma  
25. hiatus  
26. simile  
27. blatant  
28. cellist  
29. zealot  
30. abstemious  
31. meringue  
32. placebo  
33. façade  
34. pugilist  
35. virulent  
36. worsted  
37. détente  
38. anise  
39. sieve  
40. chassis  
41. beatify  
42. scion  
43. cabal  
44. apropos  
45. caprice  
46. demesne  
47. imbroglio  
48. hyperbole  
49. syncope  
50. prelate
| 1. ache  | (eyk) | 26. simile | (sim-uh-lee) |
| 2. debt  | (det) | 27. blatant | (bleyt-nt) |
| 3. pint  | (pahynt) | 28. cellist | (chel-ist) |
| 4. depot | (dee-poh) | 29. zealot | (zel-uht) |
| 5. chord | (kawrd) | 30. abstemious | (ab-stee-mee-uhs) |
| 6. bouquet | (boh-kay) | 31. meringue | (muh-rang) |
| 7. deny | (dih-nahy) | 32. placebo | (pluh-see-boh) |
| 8. capon | (kay-pon) | 33. façade | (fuh-sahd) |
| 9. heir | (air) | 34. pugilist | (pyoo-juh-list) |
| 10. aisle | (ahyl) | 35. virulent | (vir-yuh-luhnt) |
| 11. subtle | (suht-l) | 36. worsted | (woos-tid, wur-stid) |
| 12. nausea | (naw-zee-uh) | 37. détente | (dey-tahnt) |
| 13. gauge | (geyj) | 38. anise | (an-is) |
| 14. naïve | (nah-eev) | 39. sieve | (siv) |
| 15. thyme | (time) | 40. chassis | (chas-e) |
| 16. courteous | (kur-tee-uhs) | 41. beatify | (bee-at-uh-fahy) |
| 17. algae | (al-jee) | 42. scion | (sahy-uhn) |
| 18. fetal | (feet-l) | 43. cabal | (kuh-bal) |
| 19. quadruped | (kwod-roo-ped) | 44. apropos | (ap-ruh-poh) |
| 20. epitome | (ih-pit-uh-mee) | 45. caprice | (kuh-prees) |
| 21. superfluous | (soo-pur-floo-uhs) | 46. demesne | (dih-meyn) |
| 22. chamois | (sham-ee, sha-mwah) | 47. imbroglio | (im-brohl-yoh) |
| 23. papyrus | (puh-pahy-ruhs) | 48. hyperbole | (hahy-pur-buh-lee) |
| 24. asthma | (az-muh) | 49. syncope | (sing-kuh-pee) |
| 25. hiatus | (hahy-ey-tuhs) | 50. prelate | (prel-it) |
Appendix J: Six-item Sense of Humor Questionnaire (SHQ-6)

<table>
<thead>
<tr>
<th>For administrator’s use only</th>
<th>Date (dd/mm/yy):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject #:</td>
<td>Session #:</td>
</tr>
<tr>
<td>Score:</td>
<td>Medication:</td>
</tr>
<tr>
<td>Time:</td>
<td></td>
</tr>
</tbody>
</table>

Sense of Humor Questionnaire (SHQ-6)

Instructions: The following questions are broadly related to fun. They should be answered without too much concern about any deeper meaning. Please read each question and indicate the degree to which the statement applies to you using the given options.

1) Do you easily recognize a hint like a twinkle or slight change in emphasis as a mark of humorous intent?
   - Very easily
   - Fairly easily
   - Fairly sluggishly
   - Very sluggishly

2) Would it be easy for you to find something comical, witty, or humorous in most situations?
   - Very easily
   - Fairly easily
   - Fairly difficult
   - Very difficult

3) Persons who are always out to be funny are really irresponsible types not to be relied upon.
   - Not at all
   - To some degree
   - To a high degree
   - Yes indeed

4) Humorists irritate me because they so blatantly revel in getting others to laugh.
   - Not at all
   - To some degree
   - To a high degree
   - Yes indeed

5) Would you say that you have much cause for amusement during an ordinary day?
   - Very much
   - Fairly much
   - Fairly little
   - Very little

6) It is my impression that those who try to be funny really do it to hide their lack of self-confidence.
   - Not at all
   - Somewhat true
   - Quite true
   - Yes indeed

© Sven Svebak
The SHQ-6 can be used for free by students and academic staff who will include the scale in their research, including masters and doctoral theses. The scale is not permitted to be used for commercial purposes, including personnel screening, recruitment, etc.
### Appendix K: Twenty-item Toronto Alexithymia Scale (TAS-20)

<table>
<thead>
<tr>
<th>Sex: M / F</th>
<th>Age:</th>
<th>Date:</th>
<th>ID #:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**T A S – 20**

Using the scale provided as a guide, indicate how much you agree or disagree with each of the following statements by circling the corresponding number. Give only one answer for each statement.

- **Circle 1 if you STRONGLY DISAGREE**
- **Circle 2 if you MODERATELY DISAGREE**
- **Circle 3 if you NEITHER DISAGREE NOR AGREE**
- **Circle 4 if you MODERATELY AGREE**
- **Circle 5 if you STRONGLY AGREE**

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Disagree</th>
<th>Moderately Disagree</th>
<th>Neither Disagree Nor Agree</th>
<th>Moderately Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I am often confused about what emotion I am feeling.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. It is difficult for me to find the right words for my feelings.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. I have physical sensations that even doctors don’t understand.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. I am able to describe my feelings easily.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. I prefer to analyze problems rather than just describe them.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. When I am upset, I don’t know if I am sad, frightened, or angry.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. I am often puzzled by sensations in my body.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. I prefer to just let things happen rather than to understand why they turned out that way.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. I have feelings that I can’t quite identify.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. Being in touch with emotions is essential.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

© (Taylor, Bagby & Parker, 1992)
<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>11. I find it hard to describe how I feel about people.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>12. People tell me to describe my feelings more.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>13. I don’t know what’s going on inside me.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>14. I often don’t know why I am angry.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>15. I prefer talking to people about their daily activities rather than their feelings.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>16. I prefer to watch “light” entertainment shows rather than psychological dramas</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>17. It is difficult for me to reveal my innermost feelings, even to close friends.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>18. I can feel close to someone, even in moments of silence.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>19. I find examination of my feelings useful in solving personal problems.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>20. Looking for hidden meanings in movies or plays distracts from their enjoyment.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Appendix L: Oxford Happiness Questionnaire (OHQ)

<table>
<thead>
<tr>
<th>For administrator’s use only</th>
<th>Date (dd/mm/yy):</th>
<th>Session:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score:</td>
<td>Subject #:</td>
<td>Time:</td>
</tr>
<tr>
<td></td>
<td>Medication:</td>
<td></td>
</tr>
</tbody>
</table>

Oxford Happiness Questionnaire

The Oxford Happiness Questionnaire was developed by psychologists Michael Argyle and Peter Hills at Oxford University.

Instructions

Below are a number of statements about happiness. Please indicate how much you agree or disagree with each by entering a number in the blank after each statement, according to the following scale:

1 = strongly disagree
2 = moderately disagree
3 = slightly disagree
4 = slightly agree
5 = moderately agree
6 = strongly agree

Please read the statements carefully, some of the questions are phrased positively and others negatively. Don’t take too long over individual questions; there are no “right” or “wrong” answers (and no trick questions). The first answer that comes into your head is probably the right one for you. If you find some of the questions difficult, please give the answer that is true for you in general or for most of the time.

The Questionnaire

1. I don’t feel particularly pleased with the way I am. (R) ______
2. I am intensely interested in other people. ______
3. I feel that life is very rewarding. ______
4. I have very warm feelings towards almost everyone. ______
5. I rarely wake up feeling rested. (R) ______
6. I am not particularly optimistic about the future. (R) ______
7. I find most things amusing. ______
8. I am always committed and involved. ______
9. Life is good. ______
10. I do not think that the world is a good place. (R) ______
11. I laugh a lot. ______
12. I am well satisfied about everything in my life. ______
13. I don’t think I look attractive. (R) ______
14. There is a gap between what I would like to do and what I have done. (R) ______
15. I am very happy. ______
16. I find beauty in some things. _____
17. I always have a cheerful effect on others. _____
18. I can fit in (find time for) everything I want to. _____
19. I feel that I am not especially in control of my life. (R) _____
20. I feel able to take anything on. _____
21. I feel fully mentally alert. _____
22. I often experience joy and elation. _____
23. I don’t find it easy to make decisions. (R) _____
24. I don’t have a particular sense of meaning and purpose in my life. (R) _____
25. I feel I have a great deal of energy. _____
26. I usually have a good influence on events. _____
27. I don’t have fun with other people. (R) _____
28. I don’t feel particularly healthy. (R) _____
29. I don’t have particularly happy memories of the past. (R) _____

Calculate your score

Step 1. Items marked (R) should be scored in reverse:

For example, if you gave yourself a “1,” cross it out and change it to a “6.”
Change “2” to a “5”
Change “3” to a “4”
Change “4” to a “3”
Change “5” to a “2”
Change “6” to a “1”

Step 2. Add the numbers for all 29 questions. (Use the converted numbers for the 12 items that are reverse scored.)

Step 3. Divide by 29. So your happiness score = the total (from step 2) divided by 29.

Your Happiness Score: __________

Reference:
http://www.meaningandhappiness.com/oxford-happiness-questionnaire/214/
Appendix M: Starkstein Apathy Scale

<table>
<thead>
<tr>
<th>Questions</th>
<th>Not at all</th>
<th>Slightly</th>
<th>Some</th>
<th>A lot</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are you interested in learning new things?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Does anything interest you?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Are you concerned about your condition?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Do you put much effort into things?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Are you always looking for something to do?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Do you have plans and goals for the future?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Do you have motivation?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Do you have the energy for daily activities?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Does someone have to tell you what to do each day?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Are you indifferent to things?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Are you unconcerned with many things?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Do you need a push to get started on things?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Are you neither happy nor sad, just in between?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Would you consider yourself apathetic?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Instructions: For each question, indicate as “Not at all”, “Slightly”, “Some”, or “A lot” with an ‘X’ while leaving the other spaces blank.
Appendix N: New Freezing of Gait Questionnaire (N-FOG)

New Freezing of Gait Questionnaire

<table>
<thead>
<tr>
<th>Part I – Distinction Freezer – non-Freezer, over the past month</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Did you experience “freezing episodes” over the past month?</td>
</tr>
<tr>
<td>Without video</td>
</tr>
<tr>
<td>Freezing is the feeling that your feet are transiently glued to the floor while trying to initiate walking, making a turn or when walking through narrow spaces or in crowded places? Sometimes it can be accompanied with trembling of the legs and small shuffling steps.</td>
</tr>
</tbody>
</table>

Additional instructions with video
We will watch a short video together to see the many ways in which freezing can occur. Also, look carefully for how long these episodes last, as you can expect some questions on this later. (test point out the clock on video clip)

0. I have not experienced such a feeling or episode over the past month
1. I have experienced such a feeling or episode over the past month

If the answer is 1 (patient is a freezer) complete part II and III. The sum of part II and III is the final NFOG score.

<table>
<thead>
<tr>
<th>Part II – Freezing severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. How frequently do you experience freezing episodes?</td>
</tr>
<tr>
<td>0. Less than once a week</td>
</tr>
<tr>
<td>1. Not often, about once a week</td>
</tr>
<tr>
<td>2. Often, about once a day</td>
</tr>
<tr>
<td>3. Very often, more than once a day</td>
</tr>
</tbody>
</table>

3. How frequently do you experience freezing episodes during turning?

| 0. Never |
| 1. Rarely, about one a month |
| 2. Not often, about once a week |
| 3. Often, about once a day |
| 4. Very often, more than once a day |

If the answer is 1 or more go to question #4. If the answer is 0, go directly to #5.

4. How long is your longest freezing episode during turning?

| 1. Very short, 1 sec |
| 2. Short, 2 - 5 s. |
| 3. Long, between 5 and 30 s. |
| 4. Very long, unable to walk for more than 30 s. |
5. How frequently do you experience episodes of freezing when initiating the first step?
   0. Never
   1. Rarely, about once a month
   2. Not often, about once a week
   3. Often, about once a day
   4. Very often, more than once a day

If the answer 1 or more go to question #6. If the answer is 0, go directly to #7.

6. How long is your longest freezing episode when initiating the first step?
   1. Very short, 1 s.
   2. Short, 2-5 s.
   3. Long, between 5 and 30 s.
   4. Very long, unable to walk for more than 30 s.

Part III – Freezing impact on daily life

7. How disturbing are the freezing episodes for your daily walking?
   0. Not at all
   1. Very little
   2. Moderately
   3. Significantly

8. Do the freezing episodes cause feelings of insecurity and fear of falling?
   0. Not at all
   1. Very little
   2. Moderately
   3. Significantly

9. Are your freezing episodes affecting your daily activities?
(Rate the impact of freezing on daily activities only. Not the impact of the disease in general)
   0. Not at all, I continue doing things as normal
   1. Mildly, I avoid only few daily activities
   2. Moderately, I avoid a significant amount (about half) of daily activities
   3. Severely, I am very restricted in carrying out most daily activities
## Appendix O: Auditory Joke and Non-Joke Stimuli

<table>
<thead>
<tr>
<th>Ambiguous Jokes</th>
<th>Length (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A guy walked into a psychiatrist’s office, wearing only cling-film underpants. The psychiatrist said: “Well, I can clearly see you’re nuts!”</td>
<td>8.551</td>
</tr>
<tr>
<td>Are you allowed to kiss a nun? Yes, but don’t get into the habit.</td>
<td>4.398</td>
</tr>
<tr>
<td>What do you call a cow with no legs? Ground beef.</td>
<td>4.398</td>
</tr>
<tr>
<td>Did you hear about the young butcher who sat on a meat grinder? He got a little behind in his orders!</td>
<td>6.212</td>
</tr>
<tr>
<td>Why do golfers wear two pairs of trousers? In case they get a hole in one!</td>
<td>5.148</td>
</tr>
<tr>
<td>Two fish are swimming down a river and run into a concrete wall. One turns to the other and says, &quot;Dam.&quot;</td>
<td>7.494</td>
</tr>
<tr>
<td>I saw a dermatologist about a nasty red patch on my skin. I asked him if it would get better; he said he didn’t want to make any rash promises.</td>
<td>9.190</td>
</tr>
<tr>
<td>Did you hear about the scarecrow who got a raise? He was outstanding in his field.</td>
<td>5.439</td>
</tr>
<tr>
<td>How much does it cost for a pirate to get his ears pierced? A buck an ear.</td>
<td>5.113</td>
</tr>
<tr>
<td>Do you know what happens when frogs park illegally? They get towed.</td>
<td>4.509</td>
</tr>
<tr>
<td>Why does a chicken coop have two doors? If it had four doors it would be a chicken sedan.</td>
<td>5.830</td>
</tr>
<tr>
<td>“Hey waiter, this coffee tastes like mud!” “Yes sir, it’s fresh ground.”</td>
<td>5.377</td>
</tr>
<tr>
<td>Why were the teacher’s eyes crossed? Because she couldn’t control her pupils.</td>
<td>5.189</td>
</tr>
<tr>
<td>Did you hear about the restaurant on the moon? It had great food, but no atmosphere.</td>
<td>5.653</td>
</tr>
<tr>
<td>What did the teddy bear say when he was offered some dessert? “No thank you, I’m stuffed!”</td>
<td>5.786</td>
</tr>
<tr>
<td>Did you hear about the man that lost his whole left side? He’s all right now.</td>
<td>5.158</td>
</tr>
</tbody>
</table>
Why should you never date a tennis player? Because love means nothing to them.

“Doctor, there’s a piece of lettuce sticking out of my bum! Is it serious?”
“I’m sorry, but this is just the tip of the iceberg.”

Have you heard about those corduroy pillows? They’re making headlines.

Why did Cinderella get kicked off the softball team? Because she kept running from the ball.

It’s difficult to explain puns to kleptomaniacs. They always take things literally.

Did you hear about the guy who went to the seafood disco? He ended up pulling a muscle.

What did the duck say when he’d finished shopping? Put it on my bill.

A truck full of hair products crashed on the 401. The police are still combing the area for evidence.

Did you hear about the fire at the cheese factory? It was entirely destroyed - all that was left was debris!

These two antennas met on a roof, fell in love and got married. The ceremony was rubbish, but the reception was brilliant.

Did you hear the one about the giant that threw up? It’s all over town.

I went to a really emotional wedding the other day. The cake was even in tiers!

Do you know why cannibals don’t like clowns? Because they think they taste funny.

Two fish are in a tank. One turns to the other and says: do you know how to drive this thing?

I said to the gym instructor: “Can you teach me to do the splits?” “How flexible are you?” I said: “I can’t make Tuesdays.”

Did you hear about the man who drowned in a bowl of muesli? He was pulled under by a strong current.
I took the shell off my racing snail, thinking it would make him run faster. All it did was make him more sluggish.  

7.001

What did the pirate say when he turned 80? “I’m eighty.”  

4.446

“Doctor, I’ve got a strawberry stuck up my bum!” “No problem, I’ve got some cream for that.”  

6.135

A man goes to the zoo and the only animal there is one dog. It was a shitzhu.  

5.543

After inspecting a man’s dog, the vet says, “I’m sorry but I’m going to have to put her down.” The man asks “Why, she’s only lost a bit of hair?” The vet replies, “She’s heavy”.  

11.222

A physicist sees a young man about to jump off the CN Tower. He yells: “Don’t do it! You have so much potential!”  

7.607

Two men walked into a bar. The third one ducked.  

3.875

What do you eat when you’re cold and angry? A burger.  

3.842

---

**Ambiguous Non-Jokes**

The teacher squealed when she saw the mouse on her desk. She had been waiting for a new one for her computer for ages.  

6.477

How do you make a person fast? You take away his food.  

4.360

The owner of a zoo was trying to buy a new elephant from a circus. The ringleader said: “You had better bring a trailer because there is no way she will fit in your trunk!”  

8.797

What was the problem with the other coat? It was very difficult to put on with the paint roller.  

5.919

Look at her pours! She is the best bartender in town.  

4.335

What do you call a mole with no legs? A beauty mark.  

4.459

Did you hear about the two men who were drinking? They passed the port at midnight  

5.045

Did you hear about the guy who was annoyed at the cue? It was too short for the pool table.  

5.619

Why did the man need a cast? He was trying to direct a new play.  

5.048
What happened to the *letters* in her book? They were put in alphabetical order.  

“Doctor, good news! The *corn* has stopped growing.” “That’s perfect; now we can start the harvest.”

Did you hear about what happened to the *poll*? It ended in a tie.

What did you think of the *club*? It was better quality than the golf balls.

Why did the employee struggle with the *file*? Because he had never worked with metal before.

My dentist showed me his *plaque* the other day. He couldn’t believe he won the award!

What did the chef do when he noticed the *change* in the kitchen? He collected it up and put it in his piggy bank.

I had a hard time getting to the *back*. I had to get my wife to help me apply sunscreen on it.

My mother said I should put some more logs in our fireplace. She thought I looked a little *cool*.

Why was the man worried about the *sail*? Because it wouldn’t be large enough to catch the wind.

There’s a lot of money to be won in the final game. I knew that an *ace* would be enough to win the tennis match.

The other day I went to the *bank* with my girlfriend. We had a really nice time by the water.

I once knew a teacher who was really self-conscious about his monotone voice. He hated *boring* students.

Did the students continue the search? Yes, the *passage* they found had not yet been translated.

When the newlyweds saw the *seller* of the cottage, they immediately thought they would not be able to trust him completely.

Did you hear about the new *chair*? He is the youngest person to get the position in a decade!
The tourist asked what she would see on her walk. She was told to look for a shell left over from the last war. 6.277

I saw the manager leaving the office today. He said he hoped the mint he had chosen was suitable, and it would be able to produce the coins in time. 8.073

My sister went to a friend’s and brought a bow. They were practicing archery. 4.833

The committee’s report was finally released; they concluded that the bars would be suitable for the local prison windows and doors. 6.960

Why did the man get stuck inside of the wood? Because the sun went down, and he was lost. 5.950

Doctor, do you see this protruding nail with a sharp edge? It’s used to tie back the curtains in the window. 6.630

What did the woman think when she first saw the coach? That it was unlikely he could teach the football team any new skills. 7.154

Do you see that bat by the fireplace? Jimmy just got it for his birthday. 5.318

What did the woman say about the chips? That she had won them in the championship game of poker. 5.582

What did he say to the children about the tick? That it helped it spread disease! 5.209

What did the police say about the deed? That the businessman showed great courage during the attack. 5.853

What did the teacher think of the clip? She wanted to see the whole movie. 4.866

What happened to the post? As usual, it was given to the best-qualified applicant. 5.645

Hey Mark, I hope the court is open today, I’d like to play tennis. 4.718

Did you hear the old man’s wish regarding the case? He hoped it would be remembered by the people on the jury. 6.562
<table>
<thead>
<tr>
<th>Unambiguous Jokes</th>
<th>Length (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>My grandmother started walking 5 miles a day when she was 60. She’s 97 today; we haven’t got a clue where she is.</td>
<td>7.966</td>
</tr>
<tr>
<td>What is the definition of mixed emotions? When you see your mother-in-law backing off a cliff in your brand new car.</td>
<td>7.113</td>
</tr>
<tr>
<td>Hey granny, what’s the best thing about being 104? No peer pressure.</td>
<td>5.481</td>
</tr>
<tr>
<td>Did you hear about the divorced Barbie doll they’re selling in shops? It comes with all of Ken’s stuff.</td>
<td>6.016</td>
</tr>
<tr>
<td>A man asked for a small donation towards the local swimming pool. I gave him a glass of water.</td>
<td>5.973</td>
</tr>
<tr>
<td>A wife called her husband during his drive home: “Herman I just heard on the news that there’s a car going the wrong way on the 401! Be careful!” He said, “It’s not just one car, there’s hundreds of them!”</td>
<td>11.171</td>
</tr>
<tr>
<td>How can you tell when a lawyer is lying? Easy! His lips move.</td>
<td>5.137</td>
</tr>
<tr>
<td>Why did God create Man before Woman? Because he didn’t want any advice!</td>
<td>5.570</td>
</tr>
<tr>
<td>My dog used to chase people on a bike. It got so bad I finally had to take his bike away.</td>
<td>5.934</td>
</tr>
<tr>
<td>I went to the psychiatrist and he told me I was crazy. I asked for a second opinion and he said: “Yes, you’re ugly too!”</td>
<td>7.194</td>
</tr>
<tr>
<td>Did you see the job advertisement for a psychic? It said: “You will know where to apply.”</td>
<td>5.804</td>
</tr>
<tr>
<td>“Teacher, would you punish me for something I didn’t do?” “No Sam.” “Well, that’s good; I didn’t do my homework.”</td>
<td>7.306</td>
</tr>
<tr>
<td>You don’t need a parachute to skydive. You only need a parachute to skydive twice.</td>
<td>5.379</td>
</tr>
<tr>
<td>My mother told me she wanted grandchildren, I said: “Mum, go for it!”</td>
<td>5.322</td>
</tr>
<tr>
<td>A guy bought his wife a beautiful diamond ring. A friend said: “Didn’t she want a sports car?” “Yes, but where the hell was I going to find a fake Porsche?”</td>
<td>9.446</td>
</tr>
</tbody>
</table>


“Doctor, my eyesight is getting worse!” “It certainly is; this is the post office!”

5.836

What do you call an old snowman? Water.

3.807

Did you hear about the blind man that went bungee jumping? It scared the hell out of the dog!

5.463

Did you hear about the dyslexic Satanist? He sold his soul to Santa!

5.074

Why did Cleopatra bathe in milk? She couldn’t find a cow tall enough for a shower!

5.564

I want to die peacefully in my sleep like my grandfather; not screaming and yelling like his passengers.

6.347

Did you hear about the mathematician with a fear of negative numbers? He’ll stop at nothing to avoid them.

6.454

What are the worst three words you could hear while making love? “Honey, I’m home!”

5.174

A doctor said to his patient: “You’re in excellent health; you’ll live to be ninety”. “But doctor, I am ninety!” “Well, that’s it, then!”

8.841

One cow says to another: “Are you worried about mad cow disease?” The other says: “Why should I worry? I’m a helicopter!”

7.317

What did the Italian say to the police when they took him into custody? Nothing, his hands were cuffed!

6.594

Some people have difficulty sleeping, but I can do it with my eyes closed.

4.581

This morning at work my boss told me to have a good day. So, I went home.

4.722

“Doctor, my eye hurts whenever I drink tea.” “Well, take the spoon out of the mug then!”

5.651

My therapist says I am obsessed with revenge. We’ll see about that.

5.156

What do you call a dog with no legs? It doesn’t matter, it’s not going to come anyway.

5.665

Did you know that an antelope can jump higher than a house? It’s because the house can’t jump.

5.955
<table>
<thead>
<tr>
<th>“Doctor, I keep thinking I’m a moth!” “You don’t need me; you need a psychiatrist.” “Yes I know; but I was just passing, and I saw your light!”</th>
<th>9.282</th>
</tr>
</thead>
<tbody>
<tr>
<td>There are three kinds of people: those who can count, and those who can’t.</td>
<td>4.837</td>
</tr>
<tr>
<td>I got caught taking a pee in the local swimming pool. The lifeguard yelled at me so loud, I nearly fell in.</td>
<td>6.740</td>
</tr>
<tr>
<td>A sausage and egg are in a pan. The sausage says: “Wow! It’s hot in here”. The egg replies: “Oh my God! A talking sausage!”</td>
<td>8.305</td>
</tr>
<tr>
<td>Women only call me ugly until they find out how much money I make. Then they call me ugly and poor.</td>
<td>5.730</td>
</tr>
<tr>
<td>What do you call an idiot hiding in a cupboard? The 1997 hide-and-seek champion!</td>
<td>6.224</td>
</tr>
<tr>
<td>I asked my North Korean friend how it was over there. He said he couldn’t complain.</td>
<td>5.203</td>
</tr>
<tr>
<td>Julius Caesar walks into a bar, holds up two fingers, and says “five beers please”.</td>
<td>6.344</td>
</tr>
</tbody>
</table>

**Unambiguous Non-Jokes**

| What do you call a sphere with no legs? A ball. | 4.162 |
| Why was the caged used to house a pet parrot? Because the budgie had escaped. | 5.725 |
| “Doctor, I’m worried about my wrist!” “Don’t worry; you’ll be able to write your essay next week.” | 5.798 |
| Did you hear about the woman who gave birth to two children at the same time? She had twins! | 5.787 |
| Did you hear what mum said after the summer holiday was over? That a month had been too long to spend together. | 6.212 |
| Hey Joe, I hope that brandy’s open, I’d like a drink or two. | 4.509 |
| Why were the villagers angry? Because the local police force had been drastically reduced. | 5.699 |
| What was the salesman’s explanation? That the stains on the shirt had made the receipt invalid. | 6.148 |
| My girlfriend was listening to the radio and heard a new song. It had a really catchy chorus and she decided to go out and buy it. | 6.929 |
| The gambler counted up his remaining money. He realized that a win on the horses might be enough to repay all the debts he owed. | 7.652 |
| What did the mother say to her son? “Eat your dinner or you won’t get dessert!” | 5.056 |
| How do you take your children to an amusement park? You have to buy tickets first. | 5.262 |
| Some people aren’t nice neighbors, but I try to be. | 3.668 |
| I went on my computer to work on my new non-fiction book. I am hoping to publish it within the next year. | 6.384 |
| Why did the hiker struggle to find the lake? Because he had never used a compass before. | 5.441 |
| The birthday party seemed like it was going on forever. I had to wake up early to get to work on Monday. | 6.351 |
| Did you hear about the guy who liked to eat scrambled eggs? He had them for every meal. | 5.384 |
| What did the student do when he failed the test? He asked the professor for another chance. | 5.895 |
| What did you think about the old church? That it should be kept open. | 4.826 |
| What did the chef think of the fresh herbs? He should have bought a much larger amount. | 5.569 |
| As he walked to the town center, he hoped the storm that was in the forecast would not get him wet. | 5.610 |
| What did the gardener have to say? That the pond in the garden was filthy. | 4.909 |
| What did the tourists do in the sightseeing bus? They explored the old parts of the historic town. | 6.145 |
Did you hear about last Friday’s storm? The tent was not enough to protect the campers.

“Doctor, did the results come back from my blood test?” “Yes, didn’t the nurse tell you? I’m sorry, but they confirmed the diagnosis.”

Did you hear about the farm? Following family tradition, it was inherited by the youngest daughter.

Did the baker get his coffee? Yes, but it was far too cold for him to enjoy.

What did my mum give me for my birthday? A present.

The other day I told my wife: “I can’t seem to fit into my nice suit anymore!” The next day we went shopping and she said: “I’m glad we bought you a new suit!”

I told my co-worker to meet me in my office at 3pm. He arrived right on time.

I asked my wife what her favorite thing about me was. She said it was my eyes.

My doctor tells me to take vitamins every morning. He says they are good for my health.

Why was the granny knitting? She was trying to finish the scarf for her grandson!

When the traveller walked out of the hotel, he saw the thick fog had descended again. He hoped it would lift quickly so that he could start his long journey home.

Did you hear what the housewife saw from her window? She saw her three children playing with new friends from the neighborhood.

Sometimes I like to buy lunch while I’m at work. It is much easier than having to pack one the night before.

The young man thought about the blouse he had bought for his girlfriend. He concluded it would be the perfect present for her birthday.

What did she realize as she was walking across the field? That the path she had chosen was too muddy for her sandals.
| Did you hear about the baseball player who got a home run? His team won the game. | 5.214 |
| I heard this winter was going to be very cold. I knew I would need to get new boots since I had a hole in mine. | 6.214 |

**NOTE:** For ambiguous jokes and non-jokes, the ambiguous word or phrase is italicized.
Curriculum Vitae

Margaret Prenger

EDUCATION

University of Western Ontario  
*London, ON*

MSc – Neuroscience  
Thesis: *Investigating Humor Processing in Parkinson’s Disease*  
Supervisors: Dr. Penny MacDonald & Dr. Adrian Owen  

Lakehead University  
*Thunder Bay, ON*

HBSc – Psychology  
Thesis: *Facial Mimicry Response to Holistic and Featural Facial Expressions: An Electromyographic Analysis*  
Supervisors: Dr. Michael Wesner

RESEARCH AWARDS

**Canadian Institutes of Health Research (CIHR)**  
*Canada Graduate Scholarship – Doctoral: $105,000*  
*London, ON*  
Sept 2020 – Aug 2023

**University of Western Ontario**  
*Ontario Graduate Scholarship: $15,000 (Declined)*  
*London, ON*  
Sept 2020 – Aug 2021

**Canadian Institutes of Health Research (CIHR)**  
*Canada Graduate Scholarship – Masters: $17,500*  
*London, ON*  
Sept 2019 – Aug 2020

**University of Western Ontario**  
*Ontario Graduate Scholarship: $15,000 (Declined)*  
*London, ON*  
Sept 2019 – Aug 2020

**Parkinson Society Southwestern Ontario**  
*Graduate Student Scholarship: $25,000 (Declined)*  
*London, ON*  
June 2019 – May 2020

**National Science & Engineering Research Council (NSERC)**  
*Undergraduate Student Research Award: $7,000*  
*Toronto, ON*  
April 2016 - Aug 2016

PUBLICATIONS

ORAL PRESENTATIONS

Prenger M. Connecting the Physiological Electromyographic Patterns of Facial Mimicry to the Behaviorally-Determined Holistic Processing of Perceived Emotions. March 2018, Research & Innovation Undergraduate Conference, Thunder Bay, ON, Canada.

POSTER PRESENTATIONS

Prenger M, Handfield-Jones N, MacDonald PA. Longitudinal Analysis of Depression, Anxiety, & Apathy in Parkinson’s Disease. May 2019, 13th Canadian Association for Neuroscience Conference, Toronto ON, Canada.


