Pupillary Response in an Auditory Rhythm Omissions Task in Parkinson´s Disease: A Pilot Study

Frohar Sidikyar

MAPSYK360, masters program in psychology,

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Supervisor: Kjetil Vikene Department of biological and medical psychology

Abstract

When presented with short, rhythmical, musical excerpts, containing omitted beats which vary in saliency in terms of rhythmical patterns (contextual omission), and position (salience omissions), fMRI studies have shown a small effect depending on position of omission. Furthermore, when presented with auditory stimuli, a pupillary dilation response (PDR) is evoked, resulting in a pupillary peak dilation (PPD) sometime after stimulus onset. By utilizing and adapting an auditory beat-omission fMRI paradigm, to allow measurement of PDR and PPD, we used pupillometry data to investigate the effect of contextual omission (Simple vs Complex rhythm) and salience omission (O1 vs O2). We report data from a total of 25 participants, based on 45 datasets. The data were analyzed using four separate direct t-tests. We found that the omission has an effect on PPD, in that the most metrical salient omission (O1) results in a higher activation level compared to a less salient omission (O2), i.e., PPD was significantly higher in O1 simple rhythm omissions, and in O1 complex rhythm omissions, at an uncorrected threshold level.

Keywords: Parkinson's disease, omission, rhythm, pupillometry, pupil dilation.

Sammendrag

Når en presenteres med korte, rytmiske, musikalske utdrag der enkelte utelatte takter varierer i fremtredning (saliens) i form av rytmiske mønstre (kontekstuell utelatelse) og posisjon (fremtredende utelatelse), har fMRI-studier vist en liten effekt avhengig av utelatelsens posisjon. Videre, når auditivt stimuli blir presentert, fremkalles en pupillær dilatasjonsrespons (PDR), hvilket resulterer i en topp pupilledilatering (PPD) etter stimulusstart. Ved å benytte og tilpasse et tidligere fMRI-paradigme innenfor auditiv persepsjon av takt og utelatelse, for å måle PDR og PPD, brukte vi pupillometridata for å undersøke effekten av kontekstuell utelatelse (enkel vs kompleks rytme) og fremtredende utelatelse (O1 vs O2). Vi rapporterer data fra 25 deltakere, totalt 45 datasett. Dataene ble analysert ved hjelp av fire separate direkte t-tester. Vi fant at utelatelse har en effekt på PPD, der den mest metriske fremtredende utelatelsen (O1) resulterer i et høyere aktiveringsnivå sammenlignet med en mindre fremtredende utelatelse (O2), dvs. PPD var signifikant høyere ved O1 i en enkel rytme, og ved O1 i en kompleks rytme, på et ukorrigert terskelnivå.

Nøkkelord: Parkinsons sykdom, utelatelse, rytme, pupillometri, pupilldilatering

Preface

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Introduction

Over the past 200 years, the development of neurological diseases and their impact on the nervous system has gained a solid foothold in science, with neurology being strongly based on neurological examinations (Freeman & Vatz, 2010). However, with an aging population the number of individuals with neurodegenerative diseases will increase, demanding more of neurologists and neuroscience (Freeman & Vatz, 2010). A known issue when diagnosing individuals early with neurodegenerative diseases, particularly Parkinson's disease (PD), has been the lack of reliable biomarkers particularly in the pre-motor phase of the disease (Breen, Evans, Farrell, Brayne, & Barker, 2013; Rizzo et al., 2016). Pupillometry has proven to be a non-invasive, easy to measure method to investigate several cognitive processes, though only a limited number of studies has utilized the method in PD (Wang, McInnis, Brien, Pari, & Munoz, 2016). We therefor want to investigate the potential of using pupillometry as a biomarker for clinically diagnosing PD in patients and individuals at risk of developing the disease. This study is a methodological pilot, to test a paradigm which has already been used in functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) (Bengtsson et al., 2009; Færøvik, Specht, & Vikene, 2021; Geiser, Ziegler, Jancke, & Meyer, 2009; Vikene, Skeie, & Specht, 2019) and see if it is as, or even more sensitive as these two methods.

Historical background – Parkinson's disease

PD was first described in 1817 by the British physician James Parkinson (1755-1824) in the classical monography entitled "An Essay on the Shaking Palsy" (Parkinson, 2002). He recognized several non-motor features that occurred during progression of the disorder on six observed cases, such as sleep disturbance, constipation, and incontinence. More than half a century later, the French neurologist Jean-Martin Charcot (1825-1893) improved the clinical

description of the condition, and in honor of James Parkinson named it "Parkinson's Disease". Before 1975, due to a lack of various brain imaging techniques, it was challenging to classify and treat degenerative diseases in e.g., Alzheimer´s patients before they died. Patients were often diagnosed as senile, which is a collective term for multiple final phases of dementia, and the condition was considered incurable. There were also major advances in the fields of neurobiology, neurophysiology, neuro-imaging, neuroimmunology and neuro-pharmacology in the early 1900s, which led to immunological modulation for multiple sclerosis, myasthenia gravis disease, better medications for epilepsy and L-dopa for Parkinson, to mention a few (Freeman & Vatz, 2010). This dramatic change has further led to the development of several methods of brain imaging techniques such as magnetic resonance imaging (MRI), fMRI and EEG, often used in locating and identifying lesions, contributing to recent treatment and more precise neurological diagnosis (Freeman & Vatz, 2010). According to the Norwegian Institute of Public Health (2019), it is crucial to know where an individual is in their course of the disease, when assessing the extent to which the disease affects factors such as mortality, health, and quality of life. Research claims that symptoms of degenerative PD are detected in the later stages. In these stages, neurons are largely degenerated which gradually leads to neuron death. The presence of diagnostic techniques in the early stage could increase the health related quality of life in patients, and allow for identification of other disorders (Martinez-Martin, Rodriguez-Blazquez, Kurtis, & Chaudhuri, 2011; Rees, Acharya, Schrag, & Noyce, 2018), and allows the onset of early rehabilitation tailored to individual patients (Abbruzzese, Marchese, Avanzino, & Pelosin, 2015). This has aroused a great interest among scientists about what factors can promote, protect or improve the functions of PD patients.

Parkinson's Disease

PD is labeled as a neurodegenerative disease, causing progressive motor and non-motor disability, developed due to both genetic and environmental factors, leading to neuronal loss and injury, and dopamine deficiency (Homayoun, 2018). Both environmental exposure and genetic factors, and the interaction between these, are considered important contributors to PD etiology (Cannon & Greenamyre, 2012). However, it is not clear how these factors influence the PD pathogenesis, with several PD cases having no genetically identifiable cause (Ascherio & Schwarzschild, 2016). The continuous degradation and destruction of dopaminergic neurons in the Substantia Nigra pars compacta (SNpc) located in the Basal Ganglia has been identified as one of the main causes for the disease (Stergiou et al., 2009). The typical neurological damage seen in individuals suffering from PD is observable in the form of Lewy bodies (LB) and Lewy neurites (LN) as intraneuronal inclusions containing α-synuclein, a presynaptic protein believed to maintain synaptic integrity and therefor regulate synthesis of dopamine (Jain, 2010). As the disease develops and neural tissue decay, LBs are found in several structures, such as locus coeruleus, the basal and raphe nucleus and the ventral tegmental area (Capriotti & Terzakis, 2016; Ring & Serra-Mestres, 2002). However, even though studies have managed to identify neurological areas differentiating a PD brain from a regular brain, it is still unclear what are the main causes and origins of the disease. There seems to be a general agreement in the field of PD that the most important risk factor is ageing. Collier, Kanaan, and Kordower (2011) proposed that there is a common cellular mechanism seen in the degeneration of dopamine neurons and ageing in non-human primates, thus indicating that risk factors such as accumulation of cellular risk factors occurs at the same rate as the observed PD degeneration pattern. Bennett et al. (1996) performed an epidemiological study, reaching the conclusion of PD being common among the population aged 65 and up in East Boston, Massachusetts, with a positive correlation between prevalence

and age, estimating that for individuals between 65-74 years of age, 14.9 percent suffered from PD, for 75-84 years of age 29.5 percent had PD and among those older than 85, 52.4 percent had PD. Furthermore, Bennett et al. (1996) reported a twofold increase in death risk related to gait disturbance, deviations from normal walking. The increase in mortality rate among people suffering from PD was also found in a study by Morens et al. (1996).

On a genetic level, Ross and Smith (2007) present several genetic causes of PD. In the α-synuclein gene, they argue that PD is the result of the point mutation A53T, and missense mutations A30P and E46K, causing early-onset PD as early as age 55, combined with prominent dementia and poor response to L-Dopa, and they add that the duplication or triplication of α-synuclein gene can cause familial PD. In other words, variations in α-synuclein levels are to be considered contributors to the risk of developing sporadic PD. Another gene where mutations are a plausible cause of PD is LRRK2, where G2019S mutations are common in individuals with sporadic PD (1-2%), particularly if the individual is of Portuguese, North African or Ashkenazi Jewish genetic inheritance (25%). Ross and Smith (2007) state that this particular mutation in the LRRK2 gene could account for approximately 15 000 - 30 000 cases in the US. Thirdly, mutations of the protein PARKIN has been identified as a common cause of PD (Dawson & Dawson, 2010), and is linked to occurrences of early-onset recessive PD. Mutations of these proteins result in deletions or exon rearrangements, possibly involving altered degradation of proteins (Ross & Smith, 2007). Finally, it is suggested that mutations in DJ-1 and PINK1 is also a basis for developing early-onset recessive PD, though the occurrence of mutations in these genes are rare.

As for environmental causes, evidence supporting the relation between PD and exposure to pesticides has existed for a long period of time, though there has been a lack of findings suggesting either a causal connection between the two or for specific compounds of pesticides, pesticide combinations and other toxicant exposure (Brown, Rumsby, Capleton,

Rushton, & Levy, 2006). Exposure to pesticides and herbicides such as paraquat and cyperquat/MPP+, has been suggested as potential causes of sporadic PD in humans (Nandipati & Litvan, 2016; Ross & Smith, 2007). Furthermore, Dick et al. (2007) performed a case-control study of 959 cases of parkinsonism, in which 767 of said cases had PD, and a total of 1989 controls. It was concluded that there is a connection between pesticide exposure and PD, as well as an increased risk if one suffers from repetitive traumatic loss of one's consciousness. There was also a positive correlation between long term use of drugs such as antidepressants, anxiolytics and hypnotics, and family history of PD, showing higher risk of developing PD (Dick et al., 2007). Other pesticides linked with PD etiology are rotenone and organochlorines, where particularly the exposure to rotenone and paraquat in a laboratory setting often, but not always, generate PD pathology and symptomology (Nandipati & Litvan, 2016).

While many probable causes for PD have been suggested, scientists and researchers have yet to manage to craft a complete picture of how genetics and environment interact. Polito, Greco, and Seripa (2016) suggest that the reason behind few gene-environment interaction studies, may be due to limitations in sample size and issues with estimating how much of a toxicant an individual has been exposed to. The development of PD based on genetics alone is rare (Klein & Westenberger, 2012), with only 10% of the observed cases having identifiable genetic cause, indicating the importance of behavioral and environmental factors in PD pathogenesis (Ascherio & Schwarzschild, 2016). There are also studies highlighting the importance of an individual's geographic location, e.g. a higher risk of developing PD in individuals from Europe, North America and Australia, compared to individuals from Asia (Pringsheim, Jette, Frolkis, & Steeves, 2014). Another aspect of understanding how PD develops, is focusing on the gut, and how the interaction between "gut

to brain" may have an impact. However, the hypothesis that PD starts in the gut, is not strongly supported as of now, though it is in its early stages (Lionnet et al., 2018).

Epidemiology

PD is not a contagious disease, though it spreads exponentially and there are no indication of any form of immunity (Dorsey, Sherer, Okun, & Bloem, 2018). The disease can be observed regularly in the world population, ranked as the second most common neurodegenerative disease and approximately .5% of the population in the western world at the age or older than 45 are affected by it (Amato, Caverzasio, & Galati, 2020; Ascherio & Schwarzschild, 2016). In 2016 it was estimated that 1-2% of all adults over the age of 65 in the US suffered from the disease, and a total of 4% when looking at adults over the age of 80 (Capriotti & Terzakis, 2016). If one is to believe the calculations of Dorsey et al. (2007) these numbers will increase rapidly due to a worldwide increase in life expectancy. While questions have been raised on how precise these calculations are (Calabrese, 2007), an increase in the number of people affected by PD seems reasonable, as was the case with males aged 70 years and older in the state of Minnesota in the US between the years 1976-2005 (Savica, Grossardt, Bower, Ahlskog, & Rocca, 2016). There are however studies reporting a decline in prevalence of PD, in Rotterdam when comparing prevalence between 1990-2000 with the period 2000-2010 (Darweesh, Koudstaal, Stricker, Hofman, & Ikram, 2016) and from 1999 to 2009 in the UK (Horsfall, Petersen, Walters, & Schrag, 2013). Looking at the Norwegian ParkWest study, it is clear that PD in Norway seems to follow the same pattern as other Western European countries, including America, with a gender difference, where females show a delayed onset of motor symptoms, but with no differences in parkinsonism severity (Alves et al., 2009).

Symptoms of PD

Symptoms such as tremors, rigidity and bradykinesia, and identification of such motor symptoms, has for a long time been the main diagnosis criteria for PD (Berardelli et al., 2013). However, these are not the only symptoms of PD, and one may generally divide PD symptoms into motor and non-motor symptoms.

Motor symptoms. Motor symptoms of PD are symptoms which are observable as physical deficits or impairments, predominantly due to loss of dopaminergic neurons in the SNpc, which in turn has led to symptomatic therapy being focused on replacement strategies of dopamine (Schapira, Chaudhuri, & Jenner, 2017). According to Moustafa et al. (2016), these symptoms may be divided into sub-categories, with the first one being primary motor symptoms. An individual suffering from PD is likely to be moving slower than normal, and have difficulties initiating movement in general. These symptoms are known as bradykinesia, and akinesia, respectively. Other may describe a feeling of stiffness, termed rigidity, or experience tremors. Tremors may occur while resting, when performing a postural task such as stretching ones arms outwards, or while a body part is moving, a kinetic tremor (Moustafa et al., 2016).

The second category is gait impairment. The most common gait impairment among PD patients is having difficulties with lifting one's feet from the ground, hindering propulsion and a normal leg swing, which in turn leads to a shuffling gait. Other gait deficits are paroxysmal deficits, an interruption of normal gait during an ongoing motor program. These are observable as both abrupt cessation of walking, where the patients feet freeze in a position, leading to impairment of balance and often a tumble, and festination, where the patients footsteps are markedly hastened while walking (Moustafa et al., 2016).

Thirdly, Rosenblum, Samuel, Zlotnik, Erikh, and Schlesinger (2013) performed a pilot study with 20 controls and 20 PD patients, with strong indications of handwriting deficits being an early symptom of PD. Such deficits has been a recognized as potential signs of PD for many years, where several factors are included as potential signs, such as patients' ability to maintain movement velocity and the size of their writing strokes (Phillips, Bradshaw, Iansek, & Chiu, 1993), but also the peak of writing acceleration and stroke duration (H.-L. Teulings & Stelmach, 1991). Such findings led to an increased focus on handwriting and PD, giving empirical studies traction in the field from the 1990s and onwards. (Bidet-Ildei, Pollak, Kandel, Fraix, & Orliaguet, 2011; Moustafa et al., 2016). Looking at parkinsonian micrographia, a disorder expressed as abnormal reduction in ones writing size (Letanneux, Danna, Velay, Viallet, & Pinto, 2014), the researchers H. L. Teulings, Contreras-Vidal, Stelmach, and Adler (2002) investigated how visual feedback is used to control handwriting size. By manipulating the display of which the participants wrote on, they managed to also manipulate the visual size of their handwriting trace. This in turn yielded results indicating that young individuals between the age 22-31 use visual feedback in order to update their visuomotor map, elderly between the age 64-81 does so a lot less, whereas PD patients rely on the visual feedback of ongoing or previous strokes in order to program the following ones. Thus, a recursive feedback system is believed to be a part of the progressive handwriting size reduction occurring in patients with micrographia related to PD (H. L. Teulings et al., 2002).

The fourth sub-category of motor symptoms for PD are precision grip deficits, meaning formed grip limited to the thumb and index finger used to hold small objects (Moustafa et al., 2016; Napier, 1956). The index finger and thumb generate grip force, used for coupling the fingers with the object, and load force, necessary to lift the fingers (Johansson & Westling, 1984). When comparing PD patients with controls, studies show that

PD patients use more grip force when holding or lifting an object using precision grip, also requiring longer time to complete a lift, compared to the controls, reflecting the reduction of sensorimotor processing effectiveness and impairment in rate of force development (Fellows, Noth, & Schwarz, 1998).

Speech impairment is the fifth category of motor symptoms seen in PD patients (Moustafa et al., 2016), with the leading and most frequent deficit being voice impairment in the initial stages (Ho, Iansek, Marigliani, Bradshaw, & Gates, 1998). At a later stage, deficits in articulation and fluency appears, indicating that the patient has reached, or is close to reaching a severe stage of speech impairment. Such speech impairments also seem to correlate with other PD motor symptoms such as halting gait, festination and stride length (Ho et al., 1998), with rigidity and bradykinesia suggested as underlying factors resulting in speech abnormality (Robbins, Logemann, & Kirshner, 1986). Furthermore, Park et al. (2014) performed a study where they investigated the link between gait freezing and speech disturbances in PD patients, by measuring number of repetitions per sentence, speech rate and the time delay before the participants initiated speech. By comparing data from 9 PD patients with gait freezing, and 9 PD patients without gait freezing, their findings support the hypothesis that gait and speech dysfunction in PD patients share some similarities when it comes to pathophysiology (Park et al., 2014). Their findings also complement Giladi et al. (2001), stating that gait freezing development is strongly associated with speech and balance problems.

Nonmotor symptoms. Nonmotor symptoms of PD often occur before the very observable motor symptoms (Schapira et al., 2017). A challenge related to such symptoms has been to establish a common understanding of sequence and time of onset for the symptoms, and if it is a clear cut prodromal phase of sporadic PD (Hawkes, 2008). One may separate

these symptoms into four categories. These are neuropsychiatric symptoms, autonomic dysfunction, disorders of sleep and wakefulness, and others/sensory (Lim & Lang, 2010; Seppi et al., 2019). Typical neuropsychiatric symptoms are depression and anxiety, or symptoms of these. Other neuropsychiatric symptoms would be apathy, psychosis, reduced impulse control and related disorders, dementia, and other cognitive impairment. As for autonomic dysfunction, one my experience drooling, orthostatic hypotension which occurs when standing up too fast resulting in rapid blood pressure reduction, urinary, erectile or gastrointestinal dysfunction, and excessive sweating. Insomnia, sleep fragmentation, disorder during rapid eye movement sleep and excessive sleepiness during daytime are the common sleep and wakefulness disorders linked with PD. Finally, among the other symptoms are the experience of pain, fatigue, ophthalmologic dysfunction affecting vision, such as impairment of vision, and olfactory dysfunction, reduced ability to smell (Crowley, Nolan, & Sullivan, 2019; Seppi et al., 2019).

Braak Staging

A procedure often applied to trace the pathology in symptomatic and incidental cases of individuals with PD postmortem, is Braak staging (Braak et al., 2003). By examining α-synuclein-immunopositive Lewy neurites (LN), and Lewy bodies (LB) at different neuropathological sites, the authors suggest that you can classify individuals with sporadic PD in six stages, indicating how far the disease has progressed. To determine the stage of PD pathogenesis each individual belongs to, the amount of Lewy bodies in SNpc, and other extranigral areas such as dorsal motor nucleus, the vagal nerves, the raphe system, coeruleus complex, magnocellular nuclei of the basal forebrain and subnuclei located in amygdala and thalamus, are measured and compared, thus creating the neuropathological staging process based on the topography of such changes (Braak et al., 2003).

As mentioned before, there are six stages involved in Braak staging. The first stage, simply labelled stage 1, involves the dorsal motor nucleus (DMN) of the vagal nerve. Individuals at stage 1 exhibit only a few isolated LNs in this area, as well as in the intermediate reticular zone adjacent to the DMN (Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004). When reaching stage 2, the damage in DMN exacerbate and spreads to the lower raphe nuclei, the reticular formations magnocellular portions and LNs are observable in the coeruleus-subcoeruleus complex (Braak et al., 2004). Stage 3 is characterized by LNs forming in SNpc, and the appearance of LBs, pale bodies and granular aggregations within SNpcs melanized projection neurons. However, the substantia nigra is still intact, with no visible signs of neuronal loss (Braak et al., 2004). A PD patient has reached Braak stage 4 once the transition zone between neocortex and allocortex shows LNs emerging in thick networks, with smaller projection neurons in the deeper layers showing LBs (Braak et al., 2004). Finally, at stages 5 and 6, vulnerable parts of SN are showing little to none melanoneurons, which in turn makes the structure look pale compared to SN in a healthy subject if one were to inspect it. When reaching stage 5, there will be inclusion bodies in neocortex, specifically the prefrontal and high-order sensor association areas, as well as the first order association areas and premotor areas (Braak et al., 2003). At stage 6, such inclusion bodies are also present in primary fields in certain instances, resulting in severe damage in somatomotor, limbic and autonomic systems (Braak et al., 2004).

Parkinson and the Brain

As PD is a neurodegenerative disease, this essentially means that an individual with the disease will experience, and show, symptoms of progressive loss and dysfunction of neurons in the central nervous system (Amor et al., 2014). The neurodegeneration is observable in several areas of the brain, with the loss of dopaminergic neurons in the SN and

the SNpc being the most obvious pathological hallmark of PD (Balestrino & Schapira, 2020). While the degeneration of dopaminergic neurons are commonly observed in PD patients, there is evidence from early stage patients showing modulation of glutamatergic, serotonergic, noradrenergic and cholinergic neurotransmitter systems, indicating that there are several neuromodulator systems affected by the disease (Barone, 2010). Other affected areas which are considered central to developing PD are the basal ganglia, regulating the suppression and selection of competing responses (Seiss & Praamstra, 2004). There are also several studies which have found a connection between hyperactivation in ipsilateral cerebellum, linked with the deficits observed in basal ganglia, by utilizing fMRI-data (Yu, Sternad, Corcos, & Vaillancourt, 2007). Similarly, hyperactivation in primary motor and lateral premotor cortex has also been observed using fMRI (Haslinger et al., 2001), the caudal supplementary motor area, anterior cingulate cortex and parietal cortices (Sabatini et al., 2000). PD patients also express difficulties of discriminating auditory rhythms, which has been linked with basal-ganglia dysfunction, increased activity in the planum temporale and inferior parietal lobe, and high activity in motor areas and upregulation of caudate nucleus (Vikene, Skeie, & Specht, 2018). Higher activity levels when performing an automatic movement have also been observed in prefrontal cortex, precuneus, cerebellum, parietal cortex and premotor area, using fMRI (T. Wu & Hallett, 2005). The impact of PD on the brain is quite substantial, and it is therefore necessary to have a general understanding of how these areas function together.

Basal Ganglia

To further understand how PD develops and affect patients suffering from the disease, the basal ganglia play a vital part. The term basal ganglia refer to several subcortical groups of cells primarily involved in motor control, but also motor learning, emotion, executive

functions, and behavior. Utilizing a wider definition of the basal ganglia and the related nuclei, they can be further categorized as input, output and intrinsic nuclei (Lanciego, Luquin, & Obeso, 2012). First, the input nuclei consist of the accumbens nucleus, caudate nucleus and the putamen, receiving information of cortical, thalamic and nigral origin, from several different brain areas. Secondly, output nuclei consist of globus pallidus' internal segments and substantia nigra pars reticulata, sending information mainly to the thalamus. Thirdly, the intrinsic nuclei consist of globus pallidus' external segments, as well as the subthalamic nucleus and the substantia nigra pars compacta (SNpc). These nuclei relay the information between the output and input nuclei (Lanciego et al., 2012). A particularly important part of the basal ganglia is the striatum, controlling an individual's goal directed habits and actions and receives dense dopaminergic innervations from the SNpc (Zhai, Tanimura, Graves, Shen, & Surmeier, 2018). Due to these innervations, it is common to attribute the motor symptoms in PD to pathophysiology in the dorsal striatum (Zhai, Shen, Graves, & Surmeier, 2019). Furthermore, there are also indications of striatal interneurons controlling network behavior and activity, and when dopaminergic modulation of this controlling function is lost, pathophysiological driving symptoms occur (Zhai et al., 2019).

The role of substantia nigra in Parkinson's disease. PD is a neurodegenerative disease in the nervous system caused by the gradual destruction of dopaminergic neurons in the SNpc in the basal ganglia (Brundin & Lotharius, 2002; Ortuño-Lizarán et al., 2020). Studies focusing on how aging is connected with neuronal loss dates all the way back to Hodge (1894), observing changes in ganglion cells from birth till death. Fast forward seventy years, such neuronal loss was confirmed to occur in SN in several studies, however Fearnley and Lees (1991) suggested that age-related attrition of pigmented nigral cells were not to be considered an important factor in the pathogenesis (disease development) of PD.

Nevertheless, later studies have made it quite clear that degeneration of dopaminergic neurons in SN and SNpc, containing the pigment and dopamine precursor neuromelanin, are progressively observed in individuals suffering from Parkinson's disease (Morris et al., 2019). This further leads to a deficiency in dopamine levels (Lanciego et al., 2012). The SNpc is also an area where the presence of Lewy bodies (degrading neurons) is high in PD patients, and the process of neurodegeneration leads to loss of dopamine neurons, believed to result in the motor symptoms observed in PD (McGregor & Nelson, 2019). Furthermore, the damage observed in neuromelanin projecting neurons is recognized as a very important hallmark when dealing with PD (Braak et al., 2003).

Dopaminergic Pathways

To further understand the damage seen in SNpc and loss of dopaminergic neurons, one should examine dopaminergic pathways. In the case of PD, the most central pathway is the nigrostriatal pathway, which is identifiable in both patients and healthy individuals when using diffusion tensor imaging (DTI) tractography, with the nigrostriatal tract being abnormal in PD patients (Zhang et al., 2015). The nigrostriatal pathway consists of axons stretching and connecting SN with striatum both in animals and humans (Struzyna et al., 2018; Zhai et al., 2018) and through the medial forebrain bundle, reaches the dorsal striatum (Prensa, Giménez-Amaya, Parent, Bernácer, & Cebrián, 2009). Zhang et al. (2015) claims that the degradation of microstructures in the nigrostriatal tract seen in PD patients are linked with motor symptom severity, while the functional dopaminergic deficit is not as apparent, meaning that DTI may be used to potentially identify early stages of PD. Burke and O'Malley (2013) presented evidence of molecular mechanisms of degeneration of axons, highlighting the correlation between motor symptoms in PD patients and disruption the nigrostriatal-nigropallidal pathway. Furthermore, there is evidence connecting the disorganization of the nigrostriatal-

nigropallidal pathway and the amygdala-accumbens-pallidum pathways aberrant fiber coherence, showing how the limbic system could potentially be relevant to PD related motor disruption, (Guo et al., 2020).

Another dopamine pathway is the mesocortical pathway, comprised of dopaminergic projections from the ventral tegmental area of the midbrain to cortical areas and prefrontal cortex (Willing & Wagner, 2016). In the prefrontal cortex, the release of dopamine plays a vital part of several executive functions, particularly working memory, attention, cognitive flexibility, and behavioral inhibition (Willing & Wagner, 2016). While the mesocortical pathway is not the critical pathway involved in PD and PD related dopamine deficiency, abnormal activation in the mesocortical system has been linked with Parkinson gait pathophysiology (Ouchi et al., 2001). The third dopamine pathway is the mesolimbic pathway, consisting of dopaminergic neurons in the ventral tegmental area of the midbrain and projections to nucleus accumbens, allowing identification of emotionally salient stimuli, learning the associated outcomes of and responding appropriately to such stimuli (Berton et al., 2006). While the mesolimbic pathway does not seem to be as severely degraded as the nigrostriatal pathway in PD cases, Caminiti et al. (2017) reported significant axonal presynaptic degradation in early PD phases in the nigrostriatal pathway and to some extent in the mesolimbic pathway. Finally, there is the tuberoinfundibular pathway consists of dopaminergic neurons located in the hypothalamus' arcuate nucleus, projecting to the median eminence, and controls secretion of prolactin from the anterior pituitary gland (Weiner & Ganong, 1978). In the case of PD, it has been shown that dopamine neurons in the tuberoinfundibular pathway remain unaffected and do not degenerate (Benskey, Manfredsson, Lookingland, & Goudreau, 2015).

Diagnosing Patients with Parkinson

When it comes to diagnosing an individual with PD, it is common to base it on the motor symptoms and nonspecific clinical findings such as bradykinesia, tremors and rigidity, with the golden standard being the confirmation of a neurologist using neuropathological methods (Adler et al., 2014). However, the accuracy of PD clinical diagnosis has shown unsatisfactory validity, with few improvements and a lack of biomarkers providing higher accuracy when it comes to clinical diagnosis of in vivo patients (Rizzo et al., 2016). Biomarkers may be divided into three different levels, depending on what information the marker yields (Griffiths et al., 2002). Firstly, it may function as a measurable endpoint of damage to oxidized DNA bases, proteins, amino acids, and oxidized lipids. Secondly, it can be functional marker, providing physiological information such as cognitive function, blood flow and platelet aggregation. Thirdly, a biomarker may provide information about and function as an endpoint related to specific diseases such as lens opacity and vision disorders. As stated by Rizzo et al. (2016), such biomarkers are hard to come by on the matter of PD. The question then arises regarding how to advantageously use pupillometry to clinically diagnose PD.

Retinal Involvement in Parkinson´s Disease

The pupil is an opening in the center of the iris through which light enters the eye. Pupillary size can vary in response to light intensity and neurologic stimuli. Increasing brightness causes pupillary constriction while increasing darkness causes pupillary dilation, with the average diameter ranging from 2-4mm in bright light, and 4-8mm in the dark (Spector, 1990). While dilation and constriction are normal pupillary behavior, pupillary abnormalities in form of abnormal contrast sensitivity, impaired visual acuity, deficits in color vision and motion perception, have all been linked with PD, highlighting the importance of

dopamine to maintain retinal function (Archibald, Clarke, Mosimann, & Burn, 2009). Studies have also shown how PD patients show reduced pupil constriction and dilation when compared to healthy controls during the interleaved pro- and anti-saccade task (Perkins et al., 2021). This further supports the use of pupillometry as a potential biomarker for PD.

Pupillometry

Changes in pupil diameter can be utilized to observe and measure cognitive processing, and is known as pupillometry (Sirois & Brisson, 2014). The method and the pupil in general has been used as a biomarker in several studies. Matouskova, Slanar, Chytil, and Perlik (2011) used pupillometry to measure the effect of the opioid tramadol on healthy volunteers using both static and dynamic pupil parameters. Static parameters consists of pupillometry measuring initial pupil diameter, while dynamic parameters are pupillometry measuring minimal and final diameter of the pupil, time of reaching minimal diameter, reflex amplitude and one's constriction velocity (Matouskova et al., 2011). Fink, Hurley, Geng, and Janata (2018) used pupillometry in a musical context, where the pupil of the eye functioned as an index of detection of deviants and rhythmic entrainment. By presenting looping, multi-instrument rhythms, in which a rhythm is a feature of music capable of inducing specific neurological processing modes (Fink et al., 2018), participants were to respond whenever an increase in intensity occurred. Pupillary dilation was observed for all deviant rhythms, independent of whether the participants reported the deviant or not. Furthermore, Bowling, Graf Ancochea, Hove, and Fitch (2018) performed a study where they investigated the pupillary response to music with either high or low groove, high or low spectral content and syncopated or straight drum patterns. Groove is a measurement of how well musical aspects induce a subjective motivation to follow the presented beat with movement (Janata, Tomic, & Haberman, 2012). Based on their findings, Bowling et al. (2018) showed how movement

eliciting music resulted in stronger pupil dilation, indicating a connection between movement, music and pupillary response. Another study by Damsma and van Rijn (2017) utilized pupillometry in order to measure pupillary response to omissions of beats in drum rhythms, with omissions occurring at different metrical positions. Beat perception seems to be an automatic process, requiring minimum attention, and occurs in both musicians and non-musicians, stipulating how beat perception is a common cognitive ability, reflected in the pupil dilation when a surprising event such as beat omission occurs (Damsma & van Rijn, 2017). Their findings concludes that pupil dilation and pupillometry can be used as a biomarker for measuring surprise without engaging in explicit attention, but rather implicit attention. A common biomarker in this field is the event related potential (ERP) mismatch negativity (MMN), an ERP which is independent from attention and often observed in auditory oddball paradigms where a deviant sound is presented or when an expected sound is omitted, though not exclusive to auditory stimuli (Garrido, Kilner, Stephan, & Friston, 2008). Furthermore, a statistical mismatch negativity (sMMN) has been identified, reflecting how statistical learning occurs even when minimal attention is allocated to the auditory stimuli, beyond what is considered capable of one's auditory sensory memory (Koelsch, Busch, Jentschke, & Rohrmeier, 2016). Similar to MMN and sMMN, pupillometry also indicate that hierarchical beat perception requires minimal to none allocation of attention, suggesting it is an automatic process (Damsma & van Rijn, 2017).

If one were to measure cognitive processing with electroencephalography (EEG), by analyzing ERPs such as MMN and sMMN, an issue with motor-symptomatic PD patients would be the vulnerability to movement artefacts (Kline, Huang, Snyder, & Ferris, 2015). While there are methods to remove such movement artefacts (O'Regan, Faul, & Marnane, 2012), pupillometry offer an alternative as it is not as time consuming as EEG and do not necessarily require the patient to be still for longer periods of time. Exploiting the capabilities

of pupillometry has been done in some PD studies. Giza, Fotiou, Bostantjopoulou, Katsarou, and Karlovasitou (2011) used pupillometry to examine pupil light reflexes (PLR) in PD patients, exhibiting how as a non-invasive method pupillometry grants the ability to explore PLR alterations in PD patients. Their findings revealed a correlation between PD patients' PLR and clinical parameters such as disease duration, stage, and scores on motor Unified Parkinson's Disease Rating Scale (UPDRS). They further state that pupillometry could be a useful tool in the investigation of PD and other subclinical autonomic nervous system disorders (Giza et al., 2011). Stergiou et al. (2010) used pupillometry in a similar fashion to investigate PLR in PD patients, in which the parameters for the study were onset latency of constriction, baseline pupil radius, minimum pupil radius after light onset, amplitude, time for maximum miosis, maximum constriction acceleration (ACmax) and velocity (VCmax). Their results indicated VCmax and ACmax to be the most representative biomarkers to estimate central cholinergic deficiency. In another study investigating pupil size and saccadic eye movement in PD patients, to further examine the relationship between pupil size and executive function deficits, Wang et al. (2016) showed how modulation disruption of pupil size was connected to voluntary saccade preparations in PD patients. Their results yielded evidence of pupil size modulation being significantly blunted in patients with PD, which was not the case of healthy controls, thus indicating a dysfunction in anti-saccade preparatory circuits (Wang et al., 2016). Also, a study investigating dopamine and reward hypersensitivity in PD patients with and without impulse control disorder (ICD) through a simple oculomotor paradigm, utilized pupillometry as a clinical method (Drew et al., 2020). Their study demonstrated how PD patients with ICD have heightened sensitivity to exogenous monetary reward cues in general, compared to PD patients without ICD, showing only increased reward sensitivity while on dopamine medication. Drew et al. (2020) states that the simple

oculomotor paradigm they employed could potentially be used in clinical measurements to identify PD patients with risk of developing ICD and a measurement of impulsivity.

Pupillometry has been manifested as a non-invasive, cost-effective and accessible method to measure cognitive processing, when examining pupil dilations (Damsma & van Rijn, 2017). Pupil dilations has been linked with cognitive processing demands, where pupillary response increase systematically with processing load when mental resources such as memory capacity, are available. Pupillary response changes less when one reaches resource limitations, and decline when the processing of information demands resources exceeding the currently available resources (Granholm, Asarnow, Sarkin, & Dykes, 1996). Pupil dilation has also been used as a measurement of mental effort, with increased pupil dilation indicating increased mental effort to process perceived stimuli (Wolff, Scholz, Akyürek, & van Rijn, 2015), and as a measurement of cognitive effort employed in linguistic tasks such as resolving full noun phrase versus pronominal subjects, and reflexive versus pronominal objects, exemplifying how pupil dilation could be a useful tool for investigating language processing (Vogelzang, Hendriks, & van Rijn, 2016). Pupillary response has additionally been utilized as a measure of decision making, with evidence of pupil dilation occurring before an individual's decision has been openly revealed, suggesting a link between pupil dilation and release of norepinephrine (Einhäuser, Koch, & Carter, 2010). Furthermore, the pupil has also shown responsiveness to intertemporal choice, specifically when an individual is weighing pros and cons of making a decision (Lin, Saunders, Hutcherson, & Inzlicht, 2018).

By combining the use of pupillometry and the knowledge about MMN, a potential method to measure pupil response to the omission of beats in an oddball paradigm, would be the use of music, by establishing a rhythm and then at random omit certain beats (Færøvik et al., 2021; Vikene et al., 2019). There are strong indications of music appreciation being affected by violations or fulfilments of ones expectations (Huron, 2008), with Vuust,

Gebauer, and Witek (2014) arguing that these principles of anticipation in the brain are exploited in musical rhythms, resulting in the pleasure one may experience from listening to music. Rhythm itself could be defined as the interaction between what is heard and the anticipatory structuring of music in the brain, meter (Vuust et al., 2014). As for beat perception, one may further divide beats into strong and weak beats, by looking the metrical structure or meter of the presented music (Zhao, Lam, Sohi, & Kuhl, 2017). Other studies have also investigated metrical expectancy and beat perception, measuring MMN in terms of expectancy violations, in terms of beat omission or manipulation of tempo and structure (Ladinig, Honing, Háden, & Winkler, 2009; Zhao et al., 2017).

Clinical Pupillometry

Measuring pupil response is not just for scientific purposes, but has been done for many years in order to define mental state and condition of individuals in cases related to traumatic brain injury, oculomotor nerve palsy, hemorrhagic and ischemic stroke and brain death and several medical conditions such as cardiac arrest, drugs and other factors (Lussier, Olson, & Aiyagari, 2019). By examining patients with acute head injury, leading to intracranial pressure (ICP) of different levels, Taylor et al. (2003) found a strong connection between reduced pupillary constriction velocity and head injury, when patients had a mass effect and an ICP of more than 20mm Hg, ~2.7 kPa. Furthermore, ICP in general seems to affect pupillary reactivity, by simply maintaining a specific physiological position, for instance head-down tilt, resulting in decreased pupillary reactivity in healthy individuals with no present brain oedema (Soeken et al., 2018). As for loss of function in the third cranial nerve, the oculomotor nerve, in a single case study Aoun et al. (2019) examined a 53-year-old woman with severe headaches and aneurysmal subarachnoid hemorrhage. After 121 measurements of pupillary activity, they found the neurological pupil index (NPi), a

standardized algorithm for evaluating pupillary responses, preceded clinical deficits and recovery, indicating a decline 12 hours before symptoms of hemorrhage were prudent, and recovery 24 hours prior to clinical examinations would report the same. As for NPi, it has been linked to indirect damage to the brain affecting both efferent and afferent visual motor pathways, as well as reflecting direct damage to the oculomotor nerve (Aoun et al., 2019). Furthermore, an evaluation of how abnormal NPi is associated with malignant cerebral edema (MCE), in patients with acute ischemic stroke who had undergone mechanical thrombectomy, revealed MCE to be independently associated with ipsilateral abnormal NPi, suggesting that pupillometry could function as an accessible tool to monitor for MCE and supplement other methods (Dowlati et al., 2021). Pupillary response in term of size, shape, position, equality and light response are also commonly exploited when probing for conditions such as afferent pupillary defect Marcus Gunn, oculomotor paralysis, Adie's tonic pupil syndrome, Sylvian aqueduct syndrome, Horner's syndrome, Argyll Robertson pupil and essential anisocoria (Spector, 1990).

Neural Pathways in the Pupillary System

To further understand how pupillometry may actually help with PD diagnosis, we must investigate the neural pathways in the pupillary system and the human visual system.

The bones of the orbit. The human visual system consists of more than just the eyes and visual cortex. The skull is formed in a way which creates two orbits, knowns as the eye sockets (Bhatti et al., 2020). These orbits functions as specialized interconnected structures, which protect and contain the eyeballs. The unified function is to provide sight (Wilkinson, 2018). The orbit, and the bones it consists of, are often described in a pyramidical shape, angled towards the back of the skull. In more detail, the apex of the pyramidical structure points posterior medial into the optic foramen and the base is located anteriorly forming the

orbital rim (Wilkinson, 2018). There is a total of seven craniofacial bones, creating the orbit. These are the maxillary, zygomatic, frontal, lacrimal, sphenoid, palatine, and ethmoidal bones. The zygomatic, frontal, and maxillary bones are central segments of the orbital rim. The medial part of the orbital rim, consist of the lacrimal and maxillary bones, connected whit the frontal bone superiorly. As for the orbit themselves, the sphenoid, palatine, and ethmoidal bones created the cavities. The ethmoidal bone is located medially, the palatine bone in the inferiorly of the posterior orbit, and finally sphenoid bone superiorly and laterally in the orbital apex (Bhatti et al., 2020).

Alternatively, one may divide orbital bones into four sections: roof, floor, medial and lateral wall. *The roof wall* is made of the frontal bone and the sphenoid bone's lesser wing, separating the frontal sinus and the anterior cranial fossa from the orbit. It slopes backwards towards the pyramids apex, leading to the optic canal and the superior orbital fissure (Wilkinson, 2018). This fissure transmits information via the ocular motor cranial nerves; oculomotor nerve (CN III), trochlear nerve (CN IV) and abducens nerve (CN VI). Information is also transmitted via the ophthalmic division of the sensory trigeminal nerve (CN V_1), superior ophthalmic vein and the sympathetic fibers. This nerves create the gap between the greater and lesser wings of the sphenoid bone (Bhatti et al., 2020). *The orbital floor* wall consists mainly of the maxillary bone, with the palatine bone supporting the posterior part and the zygomatic bone supporting the anterolateral part. The orbital floor stretches all the way back to posterior maxillary sinus wall, which in turn hinders it from extending to the orbital apex. The floor connects anteriorly and laterally with inferior orbital fissure and infraorbital canal. the maxillary artery and trigeminal nerve is carried through the infraorbital canal, while the inferior orbital fissure separates the orbital floor from the lateral wall (Wilkinson, 2018). *The lateral orbital wall* consists of the sphenoid greater wing, the orbital process of the zygomatic bone and the zygomatic process of the frontal bone, bordering the superior and

inferior orbital fissures. The maxillary frontal process, lacrimal, sphenoid and ethmoidal bones make *the medial orbital wall*, reaching all the way to the optic canal (Wilkinson, 2018).

Anatomy and physiology of the visual system. Archibald et al. (2009) argues that visual symptoms such as reading difficulties, complex hallucination, dry eyes, and other perceptual disturbances are considerable cause of morbidity in Parkinson´s disease and functions therefore as important predictors of cognitive decline. Based on this it is therefore important to understand the underlying functions and structure of visual perception. The human visual system utilizes light as a source of information about the environment. The information is perceived through the eyes, analyzed and interpreted in several areas in the brain, for instance the visual cortex (Gupta & Bordoni, 2020). The eye itself is a multi-coated sense organ: (1) *Cornea and sclera*, forming the outer fibrous layer of connective tissue, (2) the *iris, ciliary body and choroid*, representing the middle vascular layer, and finally (3) the *retina* acting as the inner neural layer (Remington & Goodwin, 2011). The light waves are first transmitted across the transparent cornea, where the rays are redirected towards the pupil. The anterior structure iris regulates the size and shape of the pupil through two main muscles – sphincter pupillae and dilator pupillae. The sphincter pupillae muscles constrict the pupil, making it smaller. This is also known as miosis. The opposite process, mydriasis, is when the dilator pupillae muscles dilates the pupil, making it wider. In other word, the iris regulates the amount of light passing through the pupil and following lens, ultimately guiding the light towards the retina (Purves & Brannon, 2013; Remington & Goodwin, 2011).

Afferent and efferent pathways. We may further divide the visual system into major pathways, which are the afferent visual pathway and the ocular motor pathway (S. Z. Wu, Masurkar, & Balcer, 2020). The afferent visual pathway involves the retina, optic nerve, optic chiasm, optic tract and several areas of the cortex (Bhatti et al., 2020). These structures are

responsible for receiving, transmitting and processing visual information, which relates the afferent visual pathway with the sensory aspect of vision (S. Z. Wu et al., 2020). The retina is an important part of the visual system, and functions as an extension of the central nervous system (CNS). There are several specialized interconnected neurons located in this part of the eye. When light enters the eye through the pupil, photoreceptor cells located at the outermost part of retina capture the light signal, initiating a cascade of neuronal signals forwarded to the optic nerve, comprised of retinal ganglion cells and millions of nerve fibers (London, Benhar, & Schwartz, 2013). The optic nerve further extends to the lateral geniculate nucleus, thalamus and the superior colliculus located in the midbrain. From there, information is relayed to higher centers of visual processing, enabling what we perceive as visual perception (London et al., 2013). The optic nerve fibers come together and form the optic chiasm, above the sphenoid bone, which allows fibers to cross to the optic tract from the nasal retina. The chiasm thus allows immediate visual information from both eyes to be processed by both hemispheres (Kidd, 2014). Distal axons of retinal ganglion cells comprise the optic tract, which in turn due to the crossing of fibers in the optic chiasm, also consists of nerve fibers from the nasal retina of both eyes (Fraser, Newman, & Biousse, 2011). In terms of the pupillary pathway, it consists of several fibers in the optic tract. Fibers located prior to the lateral geniculate nucleus exit to the pretectal nuclei, while other fibers exit to the superior colliculi's superficial layers, via the brachium. In general, the fibers forming the pupillary pathway originate from intrinsically photosensitive retinal ganglion cells (ipRGCs), and may also affect pupillomotor input to the midbrain, originating in the retina (Bhatti et al., 2020).

The ocular motor pathway (efferent visual system) facilitate movement of the eyes, allowing an in-focus view of objects in order to capture visual information (S. Z. Wu et al., 2020). Several areas in the cerebral cortex, vestibular system, cranial nerves, and brain stem nuclei, are involved in the control of eye movement, innervating extraocular muscles, and

thus constitutes the ocular motor pathway (Tantiwongkosi & Hesselink, 2015). By utilizing pupillometry on two male rhesus monkeys, Lehmann and Corneil (2016) observed changes in the animals' pupil diameter, mainly pupil dilation, when exposed to low-levels of electrical micro stimulation of the primate frontal eye fields (FEFs). In the oculomotor system, FEFs are considered cortical components connected to the superior colliculus' intermediate layers. Thus, they claim that their results indicate changes in pupil diameter, accompany covert orienting, and that the oculomotor system could function as an alternative indicator of cognitive influence on pupil diameter (Lehmann & Corneil, 2016).

Ocular autonomic pathways: sympathetic and parasympathetic. The ocular autonomic pathway of vertebrates and autonomic innervation of their eyes is affected by pupil controlling nerves connected to both the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) (Neuhuber & Schrödl, 2010). For example, light reflex pupillometry has been utilized to investigate for dysfunction in the sympathetic and parasympathetic pupillary innervation (Dütsch, Marthol, Michelson, Neundörfer, & Hilz, 2004). The SNS and PNS are part of the autonomic nervous system (ANS), which main task is to regulate bodily functions and internal processes, in order to adapt to external and internal stressors, and maintain homeostasis in the body when possible (de Zambotti, Trinder, Silvani, Colrain, & Baker, 2018). Through the SNS and PNS, the autonomic nervous system control several ocular functions, trough postganglionic fibers originating in the pterygopalatine and ciliary ganglia, parasympathetically, and sympathetically via postganglionic fibers originating in the superior cervical ganglion (McDougal & Gamlin, 2015). Through these fibers, the ANS is able to manipulate the diameter of the pupils and ocular accommodation, by controlling several muscles in the iris and ciliary body of the eyes. Furthermore, ANS is able to influence intra-ocular pressure through the regulation of the ciliary epithelium and ciliary body blood

vessels, which in turn changes the outflow and aqueous humor formation in the eyes. Also, the ANS may control ocular blood flow by adjusting the innervations of the vasculature, blood vessel networks, in the retina, iris, ciliary body, choroid and the optic nerve (McDougal & Gamlin, 2015).

In order to further understand the role of SNS and PNS in the ocular autonomic pathways, one may look to several studies. Pupillary unrest, mainly in terms of dilation and constriction of the pupils is known as pupillary hippus (Bouma & Baghuis, 1971). To understand how SNS and PNS affect pupillary hippus, Turnbull, Irani, Lim, and Phillips (2017) performed a paired-eye control study. Their main finding revealed that by antagonizing the PNS using the pharmacological substance tropicamide, pupillary hippus is extinguished. Furthermore, using the SNS agonist phenylephrine led to dilation of the pupils, with no effect on hippus. Thus their study indicate that pupillary hippus could originate from either oscillations between PNS and SNS at the pupil, or specifically from PNS activity, regardless of SNS activity (Turnbull et al., 2017).

Pupillary Response to External Stimuli

Pupillometry is a method which measure how the autonomic nervous system controls the pupil size and the effect of external stimuli might have on the pupils. Such external stimuli could be auditory stimuli. Thus, pupillometry may also be used to measure auditory perception (Grenzebach, Wegner, Einhäuser, & Bendixen, 2021; Marois & Vachon, 2018).

Brief anatomy and physiology of the auditory system. It is not uncommon for the visual and auditory system to affect one another. One of the most studied effects of such multisensory integration is the McGurk effect (Beauchamp, 2018). The McGurk effect is considered an auditory illusion which may occur when visual syllables and incongruent auditory syllables are paired together, leading to the perception of a different syllable

(Magnotti, Dzeda, Wegner-Clemens, Rennig, & Beauchamp, 2020; McGurk & Macdonald, 1976). In terms of pupillometry, there has been increased focus on how the pupil is affected by auditory stimuli, and the pupillary response respectively (Zekveld, Koelewijn, & Kramer, 2018). In order to further understand how auditory stimuli impacts the pupil, a vital part of the visual system, the auditory system must be described. The auditory system consists of several peripheral structures known as the outer, middle and inner ear, and brain regions such as cochlear nuclei, superior olivary nuclei, lateral lemniscus, inferior colliculus, medial geniculate nuclei, and auditory cortex (Peterson & Hamel, 2018). The process of hearing has proven to be a complex, but straightforward process. When exposed to sound waves, hair cells in the cochlea transduce this energy into electrical impulses in the auditory nerve, with low-frequency sounds being phase-locked, leading to the nerves firing at a fixed point. The electrical impulse is processed ipsilateral in the ventral or dorsal cochlear nucleus, or the trapezoid body nucleus, followed by a bilateral projection to the superior olivary complex, with contralateral dominance. Through the lateral lemniscus, the signal reaches the inferior colliculus where further partial decussation occurs. Next to last, the pathway goes through the medial geniculate nucleus, finally reaching the primary auditory cortex located in the medial temporal lobe, Heschl's gyrus, for further cortical processing of the perceived auditory signal (Cope, Baguley, & Griffiths, 2015).

Pupillometry and auditory stimuli. Lewis and Bidelman (2019) performed a study in which they examined the effects of noise interference on cognitive load and perceptual identification of ambiguous vs unambiguous (categorical) stimuli, revealing that speech processing modulates behavior of the pupils. Pupil dilation increased at intermediate signal-to-noise ratio (SNR), whereas dilation levels where at a minimal at low and high SNRs (Lewis & Bidelman, 2019). In a study comparing peak pupil dilations (PPD) in hearing-

impaired vs normal-hearing participants, Ohlenforst et al. (2017) found a difference in PPD patterns across several SNRs between the impaired and the normal hearing groups. This difference is believed to indicate that hearing impaired individuals allocate cognitive resources differently than normal hearing individuals, to separate relevant sounds from noise, across different ranges of SNRs, reflected in PPD differences (Ohlenforst et al., 2017). Furthermore, pupillary dilation response (PDR) has been connected to subjective salience of noise and sounds, influenced heavily by the loudness, with white noise bursts eliciting a greater PDR than 1000Hz pure tones (Liao, Kidani, Yoneya, Kashino, & Furukawa, 2016). Pupillometry has also been utilized in studies using experimental animals, demonstrating how pupillary response functions as a reliable measurement to estimate thresholds for auditory behaviors in animal models (Montes-Lourido, Kar, Kumbam, & Sadagopan, 2021).

Pupillometry and other stimuli. Studies of the pupil reveals that this particular part of the visual system responds to many forms of stimuli, possibly with PLR and visual stimuli being the most obvious and simplest measurable response, where the pupil responds to presented light (Belliveau, Somani, & Dossani, 2019; McAnany, Smith, Garland, & Kagen, 2018). Emotional arousal has also been linked with pupillary response. By examining the effects of emotion regulating strategies on pupillary dilation, Kinner et al. (2017) found support of pupil diameter being modulated by emotional arousal, but also to mental effort in regulating autonomic emotional responses. Furthermore, it was claimed that early and late pupil dilation was influenced differently by emotional regulation, specifically two different temporal components which reflect the emotional and cognitive processes involved in regulation of emotions (Kinner et al., 2017). Pupillometry has also been used to measure alertness in hypersomnolent patients compared to controls, with indications of a connection between pupillometric variable and excessive daytime sleepiness, though not strong enough to

replace multiple sleep latency test (McLaren, Hauri, Lin, & Harris, 2002). Pupillometry has also been utilized as a measurement of memory (Kahneman & Beatty, 1966) and expected recognition modulation, in which two distinct pupillary components, early pupillary dilation amplitude and late trailing slope, reflect separate cognitive efforts (Mill, O'Connor, & Dobbins, 2016). The early components captured unexpected recognition, whereas the later components indicate general uncertainty of judgment or effort.

When presented with an olfactory stimulus, pupil dilation occurs indicating the activation of the sympathetic nervous system (Schneider et al., 2009). This claim has been further investigated and confirmed by Aguillon-Hernandez et al. (2015), reporting an association between stimuli intensity and pupil dilation, and that the absence of olfactory stimulation showed decreased pupil dilation levels. Furthermore, when a corresponding visual stimulus is present when olfactory stimuli is presented, this also induce a rapid focus of the gaze towards the visual stimuli. This in turn suggests that olfactory stimulation increase the activity of the sympathetic system, which leads to pupillary dilation (Aguillon-Hernandez et al., 2015).

When presented with a somatosensory stimuli, i.e. touch, pupil size has been investigated in pain studies, revealing pupillary pattern response in cluster headache patients with an absent miosis, compared to controls, in response to the cold pressor test (Tassorelli et al., 1998). Another study performed pain induction by the use of ice spray, to measure pupillary response to pain, during both a hypnotic and non-hypnotic state, revealing a significantly smaller pain related pupil dilation during hypnotic state, compared to non-hypnotic state, as well as reduced pupil oscillations during hypnosis (Walter, Lesch, Stohr, Grunberger, & Gutierrez-Lobos, 2006). Furthermore, when inducing pain using a pressure algometer, immediately after pain onset, pupil dilation occurs, with the pupillary response correlating positively with pressure intensity 10 seconds after pressure onset to pressure

offset, stipulating how pupillometry could be utilized to measure pressure pain intensity (Höfle, Kenntner-Mabiala, Pauli, & Alpers, 2008). However, in a recent study, van Hooijdonk et al. (2019) investigated the effects of affective and non-affective stroking had on pupil dilation, suggesting that while pupil dilation is a response to tactile input, it is not necessarily due to specific C-tactile stimulation, but the arousal spawned by stimulus intensity changes.

Pupil size: locus coeruleus – norepinephrine system. Changes in pupil size such as pupil dilation has been known to reflect surprise (Damsma & van Rijn, 2017), it has been linked with the time course of decision-making and autonomic arousal prompted by characteristics of the stimuli (Oliva & Anikin, 2018; van Hooijdonk et al., 2019). In other words, pupil dilation is a response linked with expectations (Friedman, Hakerem, Sutton, & Fleiss, 1973; Steinhauer & Zubin, 1982), and also been suggested to reflect locus coeruleus (LC) brain activity (Laeng, Sirois, & Gredebäck, 2012). The LC is a nucleus of the brainstem, forming the norepinephrine system's hub, commonly labeled the locus coeruleus-norepinephrine (LC-NE) system (Aston-Jones & Cohen, 2005) and the neurons in this part of the brainstem are the only ones producing norepinephrine (Sara, 2009). By investigating several modeling and neurophysiological studies of monkeys, Aston-Jones and Cohen (2005) suggested that LC neurons display phasic and tonic activity. Tonic LC activity was shown when task utility wanes, when the task was disengaging and alternative behaviors were explored, whereas phasic LC activity was prevalent when task-related decision processes were engaged, facilitating ensuing behaviors to increase performance related to the task. The functions of the two LC activation modes created the basis for an adaptive gain theory of the LC-NE system, which suggests the LC-NE system to interact with several brain circuits in the anterior cingulate cortices, the bitofrontral cortices and the dopamine system (Aston-Jones & Cohen, 2005). Furthermore, LC neurons respond to stimuli salience and biological

significance, and therefor are rather sensitive to behavioral contexts requiring behavioral adaptation and shift in attention (Sara, 2009). With electrophysiological data showing LC responding to changes of stimulus relevance before the forebrain regions are activated, preceding changes in adaptive behavior, the LC-NE system's position in adapting behavior and shifting attention towards relevant stimuli is reinforced (Sara, 2009). In terms of individuals with PD, autopsies have shown that Lewy pathology has been developed in the LC of post-mortem PD patients with sporadic neuropathological PD, but not in the matching controls (Del Tredici & Braak, 2013). Based on the LC-NE system's role in attention, and how it affects pupil dilation and expectation, this could indicate that pupil dilation could be somewhat different in sporadic PD patients, compared to healthy controls.

Goal of the Study

This study further examined a paradigm previously used in two fMRI studies, which included individuals with PD and healthy individuals (Færøvik et al., 2021; Vikene et al., 2019). The previous studies investigated whether fMRI would be sensitive enough to register differences in various forms of beat omission, in terms of rhythmic patterns (contextual omission) and position (salience omissions). In these studies, they found no main effect of metric complexity for omission or normal presentation, nor any interaction effects between the two. In one of the studies however, there was evidence for omission position having a small effect at an uncorrected threshold, more specifically the first omission, the most metrical salient one, showing higher activation levels in medial superior frontal gyrus and anterior cingulate gyrus (Færøvik et al., 2021).

Based on previous research using pupillometry and beat salience, which indicate that pupillometry is sensitive to auditory manipulations, we wanted to test if pupillometry would be sensitive enough to pick up potential differences in the paradigm previously used in fMRI.

The end goal of this pilot study was to establish whether the paradigm then can be used in further studies on Parkinson's disease. More specifically, whether pupil dilation is sensitive enough to register differences in beat omission, in terms of rhythm pattern (contextual omission) and location (salience omission). The null hypothesis (H0) of this study states that contextual and salience omission of beats elicit no change in a healthy individuals' pupil diameter, when omission occurs at an unexpected time. The alternative hypothesis (H1) states that contextual and salience omission of beats affects and changes the pupil diameter in healthy individuals when the presented rhythm is expected, but omission is unexpected.

Methods

Participants

We recruited 40 Norwegian individuals to participate in the study as healthy controls. They were recruited through fliers, social media, and word of mouth. The age of the participants spanned from 19 to 30 years old (M = 24.20, SD = 2.94). Participants reported no loss of hearing or hearing impairment, no neuropsychological conditions and were not under the influence of any drugs or medications during, and 48-hours prior to testing. Due to incomplete data, technical issues and lighting challenges, a total of 15 participants were excluded. With this in mind, we report data from a total of 25 participants (14 male, 11 female, M = 24.96, SD = 2.92). Data were gathered from both left and right pupils, yielding 50 datasets, of which five were excluded, predominantly due to loss of signal in more than 80% of the recording (three right, two left). This leaves a total of 45 datasets which were cleaned for eyeblink artefacts.

Ethics

The regional committee for medical and health research ethics Vest approved the study under REK VEST 2017/1171. The study received ethics approval from the University of Bergen. In accordance with the declaration of Helsinki and in order to volunteer for the study, all participants read and signed an informed consent form. Participants were compensated with 100NOK.

Apparatus

Auditory stimuli were presented by a Micromate 304 Screening Audiometer to check for any hearing impairment. Pure tones, with a frequency of 1000, 2000, 4000, 6000 and 8000 Hz at a sound pressure level of 30 decibel, were presented. During testing, participants would

sit down in a stationary chair, in a room with a lighting level of ~50 lux. Auditive stimuli were presented through a pair of Sennheiser HD600 headphones, at a sound pressure level of 70 decibel. Participants would focus their vision on a fixation point on a white wall, 1.5meters away during testing. All data were recorded by an Intel® Core™ i7 – 1065G7 CPU @ 1.30GHz 1.50GHz computer, on a Microsoft Windows 10 system with 16GB RAM. Pupil diameters were measured using a Pupil Labs w120 e200b binocular eye tracking headset produced by Pupil-Labs, fitted with a nose support and two eye cameras. Data recording was done using the software Pupil Capture v2.5.0, Pupil Player v2.5.0 and Pupil Service v2.5.0. This is an open-source program, in which we wrote a script (PheDer), in Visual Basic in order to present auditory stimuli and record pupil diameter simultaneously. PheDer sampled images with a resolution of 100hz, with 10ms between each registration. During testing, auditive stimuli were presented by the same hardware which recorded pupil data.

Stimuli

A baseline measurement was performed with no auditory stimuli present. Participants were instructed to focus on the fixation point on the wall. Following the baseline session, in a randomized order, participants were presented with short rhythmic musical excerpts, totaling 10 blocks of one minute and 44 seconds each, with a short break of 13~16 seconds between blocks. Each block consisted of rhythms of 120 beats per minute (bpm), in a common meter (4/4-tempo), with two different degrees of complexity. During the first part of a block, the particular rhythm was established, either a simple or complex rhythm. Temporal position of omission could be either the first (O1) or second (O2) beat of the rhythm (See fig 1). In each block, the established rhythm was presented 36~38 times, with six beat omissions in each block. The order of rhythm and omissions was quasi randomized. Participants would focus on the fixation cross on the wall during testing. The experimental design is a simplification of a

former auditory beat-omission fMRI paradigm used to examine whether PD patients show abnormal activation when processing rhythm and omission (Vikene et al., 2019) and also replicated to investigate omission activation and repetition suppression with in healthy participants (Færøvik et al., 2021).

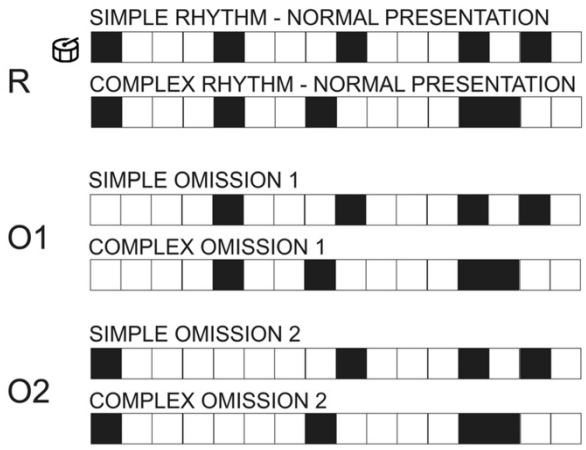

Figure 1. The design of the omission paradigm. The omission paradigm was presented in a total of 12 blocks. R was divided in two normal presentations of rhythm: simple and complex. O1 and O2 represented beat omissions at position 1 or 2.

Operationalization of Variables

In this study there were a total of two independent variables, O1 and O2. Both of these variables had two separate levels, simple or complex. This leaves us with a 2x2 within subjects' experimental design, which normally would be analyzed using an Anova. However, it was decided beforehand that four separate direct t-tests would be preferable.

Procedure

Data acquisition was performed at the department of Medical and Biological psychology (IBMP), University of Bergen, in a soundproof audio laboratory. All participants received and filled out consent forms prior to the study, which included details about the goals

of the study, their rights as volunteers and privacy policy. To avoid any distractions during testing, all participants were instructed to remove any disruptive objects (i.e., mobile phones, smart watches, purses, outerwear). In the laboratory, there was a section designed to sit down and fill out questionnaires, with the pure-tone audiogram in due vicinity to carry out the following hearing tests to ensure all participants had normal hearing. Participants signaled with a clear "yes" whenever they heard a sound and remained silent when no sounds were perceived. After confirmation of normal hearing, experimental testing ensued.

The testing area consisted of a chair facing the wall with the fixation point, a desk accommodating the pupillometry equipment, and computer. The desk was positioned behind the chair to avoid any distractions during testing. Light at eye height for the participants was measured by a luminance meter to be ~50 lux. All participants received brief instructions before testing. While in the testing area, the Pupil Core headset had to be adapted to each participant individually, to make sure that the eye cameras measured the pupil diameter and would not fall off during testing. Participants were instructed to get into an agreeable and natural position in the chair, focusing on the fixation cross on the wall without moving their head. A baseline session was performed to measure the size of the pupil without any interfering stimuli present. Following the baseline session, participants were told not to speak during testing unless they wanted to abort the experiment. Testing ensued with the presentation of musical excerpts. While participants were tested, a live feed of the pupil is sent to the connected computer, which allows the experimenter to observe and monitor the session.

When testing started, all 10 blocks were presented as described earlier. At no point in time did the experimenter need to intervene, until data acquisition had been finished. Once the rhythm omission data had been gathered, a hearing effort test followed. Before starting the test, each participant was informed that the next session will no longer contain music, but

instead there would be a sentence of five words. The task was to listen to the sentence uttered and repeat the sentence or the words they heard. Eventually, there would be several types of distractors and noise, making the task increasingly more difficult. Another baseline session ensued, to make sure that the Pupil Core eye cameras were measuring the pupil diameter. The testing session was initiated. The experimenter had to check and note the words which the participant uttered, keeping track of how many correct words they managed to identify for each sentence. The hearing effort test data are not further examined in this thesis.

Results

Pupillometry data

The pupillometry data were analyzed using R. Figures were produced using ggplot in R, with LOESS smoothing and a span of .5. Compared conditions with simple rhythm are normal presentation (SRN), omission position 1 (SR1), omission position 2 (SR2). Compared conditions with complex rhythm are normal presentation (CRN), omission position 1 (CR1), omission position 2 (CR2). We performed preplanned two-sided t-test for all omissions with the corresponding normal presentation in order to investigate significance levels of PPD/PDR in omitted conditions (SR1, SR2, CR1, CR2) compared to normal conditions (SRN, CRN). The following results have not been corrected for multiple comparison.

Simple rhythm. Two-sided t-test (SRN,SR1), revealed a significant difference in peak dilation between conditions SRN and SR1 (M = 0.04 vs. 0.598, SD = 2.21 vs. 2.69), t (219.36) = 2.83, p = 0.005, d = 0.23, 95% CI [-0.95, -0.17], with peak dilation reached 740ms after stimulus onset for SR1. For conditions SRN and SR2, t-test (SRN, SR2) revealed a non-significant difference in peak dilation (M = 0.011 vs. 0.285, SD = 2.30 vs. 2.34), t (311.89) = 1.78, p = 0.077, d = 0.12, 95% CI [-0.58, 0.03] . Peak dilation was reached 790ms after stimulus onset for condition SR2.

Complex rhythm. Two-sided t-test (CRN, CR1), revealed a significant difference in peak dilation between conditions CRN and CR1 (M = -0.041 vs. 0.273, SD = 2.21 vs. 2.38), t (303.1) = 2.07, p = 0.039, d = 0.14, 95% CI [-0.61, -0.02], with peak dilation reached 760ms after stimulus onset for CR1. For conditions CRN and CR2, t-test (CRN, CR2) revealed a non-significant difference in peak dilation (M = -0.011 vs. 0.192, SD = 2.76 vs. 2.91), t

(369.38) = 1.76, $p = 0.079$, $d = 0.11$, 95% CI [-0.65, 0.04]. Peak dilation was reached 1200ms after stimulus onset for condition CR2.

Pupil diameter change over time. The data described above is visualized in figure 2, where each line is color coded based on the presented condition. LOESS .5 smoothing was utilized to manufacture a smoother, but less precise visual representation of the data due to the averaging of each measurement point, in comparison to the former statistical analysis. Furthermore, data was transformed so that dilation = 0mm at pattern onset, in order to visualize changes in relative numbers. Significant differences from baseline SRN (cyan) and CRN (red) were found for conditions SR1 (blue) and CR1 (gold) in figure 2. Conditions SR2 (magenta) and CR2 (green) were not significant. A thick blue line marks the time period of SR1 being significantly different from SRN at $p < 0.05$. A thick gold line marks the time period of CR1 being significantly different from CRN at $p < 0.05$. While the other two conditions yielded insignificant results, the order of peak dilation values follow the hypothesized order, ranking the highest peak first: SR1, CR1, SR2, CR2.

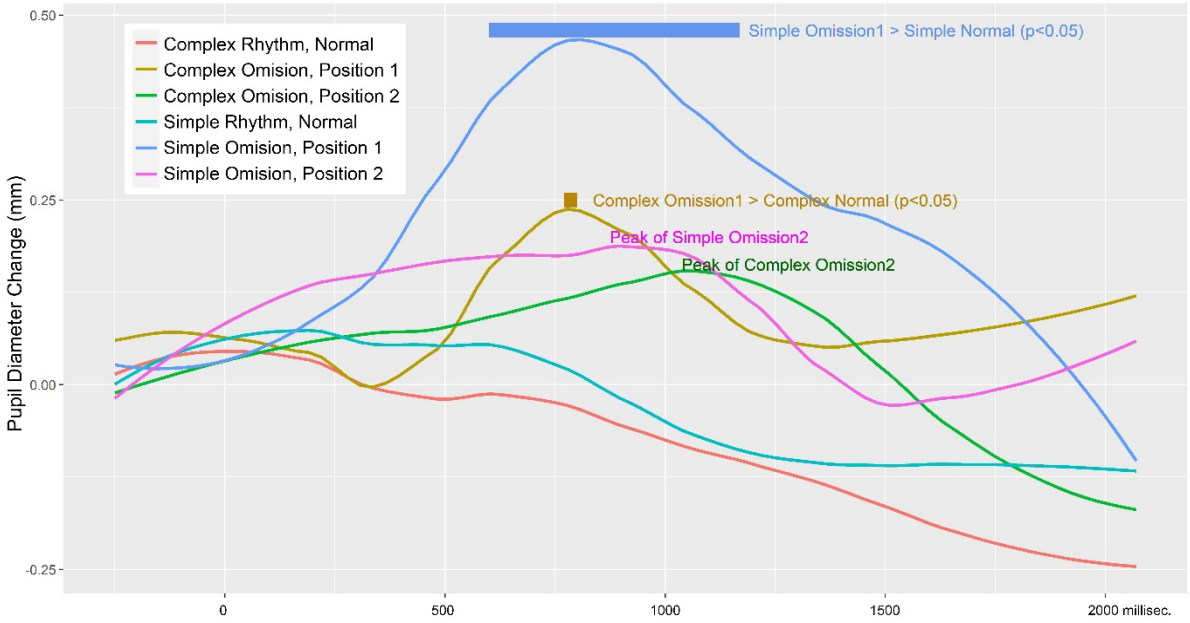

Figure 2. Shows change in pupillary diameter measured in mm, from -250ms before and 2200ms after stimulus onset for all conditions.

Discussion

In this methodological pilot study, we report differences in PDR and PPD between several conditions to omitted auditory stimuli, in terms of contextual and salience omission. For all conditions with omission, PDR was reported immediately after stimulus onset, with PPD occurring between 740-1200ms after stimulus onset. For trials with no omission of stimuli, no PDR was reported. Significant differences in PDR between trials, with and without omission, were found for the most salient omissions in both rhythms (O1). These results are as expected when looking at former studies on pupillometry and auditory stimuli (Damsma & van Rijn, 2017; Fink et al., 2018), however the highest PPD occurred in the simple rhythms. This indicates that the paradigm is sensitive enough to differentiate between the conditions, which has not been the case in former MR-studies utilizing the same paradigm (Færøvik et al., 2021; Vikene et al., 2019).

When comparing all conditions, PPD was larger for condition SR1, eliciting a pupillary dilation increase at .45mm occurring 740ms after stimulus onset. It is possible that the participants were more surprised by the omission of that particular beat, as pupillary dilation has been known to reflect surprise (Damsma & van Rijn, 2017). Furthermore, the stronger PDR and larger PPD could indicate that the individual is more surprised by the omitted stimuli at position one, compared to position two in the simple rhythm, and compared to the complex rhythm in general. This does support the findings of Damsma and van Rijn (2017), in that the omission of a salient first beat elicits a larger PPD than omission of a second beat considered less salient. Interestingly, early PPD has been known to capture unexpected recognition (Mill et al., 2016), it is thus possible that the omission at position one beats are more unexpected than omission of position two beats.

As former studies have shown, the current methods for clinically diagnosing PD has shown unsatisfactory validity, and has been suggested to be inaccurate (Adler et al., 2014; Rizzo et al., 2016). Several studies have investigated changes on PLR in PD based on pupillometry (Giza et al., 2011; Stergiou et al., 2010). Furthermore, pupillometry has been used to investigate the effects of a wide variety of stimuli, particularly auditory stimuli (Damsma & van Rijn, 2017; Lewis & Bidelman, 2019; Liao et al., 2016; Montes-Lourido et al., 2021; Ohlenforst et al., 2017). However, investigating the effects of auditory stimuli on PDR and PPD in PD patients are, to the best of our knowledge, unexplored. The results of the present study indicate that the most prominent and strongest effect, albeit a small effect size, occurs during the most salient and contextual omission, SR1 trials. This provides a reason to perform the same paradigm with PD patients and compare the data with the healthy controls, both younger and the same age. If the results are significantly different in any way there is cause to further explore the possibility of using pupillometry measurements based on rhythm pattern and location as an additional tool when clinically diagnosing PD in earlier stages, as a supplement to the current main diagnosis criteria (Berardelli et al., 2013). Furthermore, one could investigate if PDR and PPD differentiates between early, mid and late-stage PD in vivo patients, which has been heavily based on pathology tracing post mortem based on LNs and LBs (Braak et al., 2003).

Finally, the low cost and non-invasive nature of pupillometry makes it a suitable alternative to many other techniques (Damsma & van Rijn, 2017; Giza et al., 2011; Wang et al., 2016). It also does not suffer from the same limitations, unpleasantries, resource demand or strict exclusion criteria as seen in fMRI, EEG, and magnetoencephalography. As individuals at risk of developing PD are at the age of 45 and up (Amato et al., 2020; Ascherio & Schwarzschild, 2016), pupillometry could possibly offer an additional scientific approach of early detection of PD. The benefits of being able to detect PD in earlier stages, could

potentially provide the option of implementing early measures to slow down degradation, which in turn could promote further research and identify potential causes of the disease, which is still disputed regarding the role of genetics and environmental factors.

Limitations of the Study

As this study is considered a pilot study, there are several limitations which we will address. Looking at the design and the order of beats in the simple rhythm, the omitted beat in position one could be affected by the last two beats which are closer in temporal position compared to the first three, that is, in SR1 trials the omitted beat is perceived as the third beat in a row of three closer beats, followed by two beats further apart in time (see figure 3). In other words, the previous presented beats build expectations for the third beat. Thus, the expectation of the third beat being presented, which in turn is actually omitted, led to a stronger PDR than the other conditions. This would support former studies linking pupillary response with expectation (Friedman et al., 1973; Steinhauer & Zubin, 1982).

Original SRN	X				X				X				X		X	
Perceived SRN	X		X		X				X				X			
Original SR1	O				X				X				X		X	
Perceived SR1	X		X		O				X				X			

Figure 3. Shows how SRN and SR1 trials originally and alternatively could be perceived.

Another limitation would be the low effect size in all conditions. Only for condition SRN/SR1 was effect size reported above the 0.2 threshold of a small effect size. It is not unlikely that light conditions could be an important variable affecting these results, since the

pupils are naturally very light sensitive, although this is purely speculation. However, it could be of interest to perform the study under different light conditions.

Thirdly, as mentioned, the results were analyzed through preplanned two-sided t-tests, which did not include correction for multiple comparison. However, for the sake of interest, if the results had been corrected for multiple comparison, only the results from SRN/SR1 would pass the $p < .05$ threshold. While this would argue that CRN/CR1 should be deemed insignificant along with SRN/SR2 and CRN/CR2, it also strengthens the argument of SRN/SR1 significance.

Conclusion

Based on the findings of this study, pupillometry is a method suitable for measuring the effects that contextual and salience omission of beats has on pupil diameter in healthy individuals. With clear differences in terms of PDR, when comparing trials with and without omission, the unexpected omission generate a dilation of the pupils, with a stronger PDR and larger PPD for trials where the rhythm is simple. As no particular PDR was reported for the condition SRN and CRN, but was present in conditions SR1, SR2, CR1 and CR2, pupillometry may be utilized to measure the pupillary response to unexpected changes in auditory stimuli. How pupillometry may be utilized as a tool for diagnosing early PD will require data from PD patients and further research.

References

Abbruzzese, G., Marchese, R., Avanzino, L., & Pelosin, E. (2015). Rehabilitation for Parkinson's disease: Current outlook and future challenges. *Parkinsonism Relat Disord, 22*, S60-S64. doi:10.1016/j.parkreldis.2015.09.005

Adler, C. H., Beach, T. G., Hentz, J. G., Shill, H. A., Caviness, J. N., Driver-Dunckley, E., . . . Dugger, B. N. (2014). Low clinical diagnostic accuracy of early vs advanced Parkinson disease: Clinicopathologic study. *Neurology, 83*(5), 406-412. doi:10.1212/WNL.0000000000000641

Aguillon-Hernandez, N., Naudin, M., Roché, L., Bonnet-Brilhault, F., Belzung, C., Martineau, J., & Atanasova, B. (2015). An odor identification approach based on event-related pupil dilation and gaze focus. *Int J Psychophysiol, 96*(3), 201-209. doi:10.1016/j.ijpsycho.2015.03.009

Alves, G., Müller, B., Herlofson, K., HogenEsch, I., Telstad, W., Aarsland, D., . . . Larsen, J. P. (2009). Incidence of Parkinson's disease in Norway: the Norwegian ParkWest study. *J Neurol Neurosurg Psychiatry, 80*(8), 851-857. doi:10.1136/jnnp.2008.168211

Amato, N., Caverzasio, S., & Galati, S. (2020). Clinical implication of high-density EEG sleep recordings in Parkinson's disease. *J Neurosci Methods, 340*, 108746-108746. doi:10.1016/j.jneumeth.2020.108746

Amor, S., Peferoen, L. A. N., Vogel, D. Y. S., Breur, M., van der Valk, P., Baker, D., & van Noort, J. M. (2014). Inflammation in neurodegenerative diseases-an update. *Immunology, 142*(2), 151-166. doi:10.1111/imm.12233

Aoun, S. G., Welch, B. G., Cortes, M., Stutzman, S. E., MacAllister, M. C., El Ahmadieh, T. Y., . . . Olson, D. M. (2019). Objective Pupillometry as an Adjunct to Prediction and Assessment for Oculomotor Nerve Injury and Recovery: Potential for Practical Applications. *World Neurosurg, 121*, e475-e480. doi:10.1016/j.wneu.2018.09.140

Archibald, N. K., Clarke, M. P., Mosimann, U. P., & Burn, D. J. (2009). The retina in Parkinson's disease. *Brain, 132*(5), 1128-1145. doi:10.1093/brain/awp068

Ascherio, A. P., & Schwarzschild, M. A. P. (2016). The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol, 15*(12), 1257-1272. doi:10.1016/S1474-4422(16)30230-7

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function : Adaptive gain and optimal performance. *Annu Rev Neurosci, 28*(1), 403-450. doi:10.1146/annurev.neuro.28.061604.135709

Balestrino, R., & Schapira, A. H. V. (2020). Parkinson disease. *Eur J Neurol, 27*(1), 27-42. doi:10.1111/ene.14108

Barone, P. (2010). Neurotransmission in Parkinson's disease: beyond dopamine. *Eur J Neurol, 17*(3), 364-376. doi:10.1111/j.1468-1331.2009.02900.x

Beauchamp, M. S. (2018). Introduction to the special issue: forty years of the mcgurk effect. *Multisensory research, 31*(1-2), 1-6.

Belliveau, A. P., Somani, A. N., & Dossani, R. H. (2019). Pupillary light reflex.

Bengtsson, S. L., Ullén, F., Henrik Ehrsson, H., Hashimoto, T., Kito, T., Naito, E., . . . Sadato, N. (2009). Listening to rhythms activates motor and premotor cortices. *Cortex, 45*(1), 62-71. doi:10.1016/j.cortex.2008.07.002

Bennett, D. A., Beckett, L. A., Murray, A. M., Shannon, K. M., Goetz, C. G., Pilgrim, D. M., & Evans, D. A. (1996). Prevalence of Parkinsonian Signs and Associated Mortality in a Community Population of Older People. *N Engl J Med, 334*(2), 71-76. doi:10.1056/NEJM199601113340202

Benskey, M. J., Manfredsson, F. P., Lookingland, K. J., & Goudreau, J. L. (2015). The role of parkin in the differential susceptibility of tuberoinfundibular and nigrostriatal

dopamine neurons to acute toxicant exposure. *Neurotoxicology, 46*, 1-11. doi:10.1016/j.neuro.2014.11.004

Berardelli, A., Wenning, G. K., Antonini, A., Berg, D., Bloem, B. R., Bonifati, V., . . . Vidailhet, M. (2013). EFNS/MDS-ES recommendations for the diagnosis of Parkinson's disease. *Eur J Neurol, 20*(1), 16-34. doi:10.1111/ene.12022

Berton, O., McClung, C. A., DiLeone, R. J., Krishnan, Renthal, W., Russo, S. J., . . . Nestler, E. J. (2006). Essential Role of BDNF in the Mesolimbic Dopamine Pathway in Social Defeat Stress. *Science, 311*(5762), 864-868. doi:10.1126/science.1120972

Bhatti, M. T., Biousse, V., Bose, S., Danesh-Meyer, H. V., Falardeau, J., Levin, L. A., . . . Williams, Z. R. (2020). *Basic and Clinical Science Course, Section 5: Neuro-Ophthalmology* (2020-2021 ed. Vol. Section 5). USA: American Academy of Ophthalmology.

Bidet-Ildei, C., Pollak, P., Kandel, S., Fraix, V., & Orliaguet, J.-P. (2011). Handwriting in patients with Parkinson disease: Effect of l-dopa and stimulation of the sub-thalamic nucleus on motor anticipation. *Hum Mov Sci, 30*(4), 783-791. doi:10.1016/j.humov.2010.08.008

Bouma, H., & Baghuis, L. C. J. (1971). Hippus of the pupil: Periods of slow oscillations of unknown origin. *Vision Res, 11*(11), 1345-1351. doi:10.1016/0042-6989(71)90016-2

Bowling, D. L., Graf Ancochea, P., Hove, M. J., & Fitch, W. T. (2018). Pupillometry of Groove: Evidence for Noradrenergic Arousal in the Link Between Music and Movement. *Front Neurosci, 12*, 1039-1039. doi:10.3389/fnins.2018.01039

Breen, D. P., Evans, J. R., Farrell, K., Brayne, C., & Barker, R. A. (2013). Determinants of delayed diagnosis in Parkinson's disease. *J Neurol, 260*(8), 1978-1981. doi:10.1007/s00415-013-6905-3

Brown, T. P., Rumsby, P. C., Capleton, A. C., Rushton, L., & Levy, L. S. (2006). Pesticides and Parkinson's Disease-Is There a Link? *Environ Health Perspect, 114*(2), 156-164. doi:10.1289/ehp.8095

Brundin, P., & Lotharius, J. (2002). Pathogenesis of parkinson's disease: dopamine, vesicles and α-synuclein. *Nat Rev Neurosci, 3*(12), 932-942. doi:10.1038/nrn983

Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res, 318*(1), 121-134. doi:10.1007/s00441-004-0956-9

Braak, H., Tredici, K. D., Rüb, U., de Vos, R. A. I., Jansen Steur, E. N. H., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging, 24*(2), 197-211. doi:10.1016/S0197-4580(02)00065-9

Burke, R. E., & O'Malley, K. (2013). Axon degeneration in Parkinson's disease. *Exp Neurol, 246*, 72-83. doi:10.1016/j.expneurol.2012.01.011

Calabrese, V. P. (2007). Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology, 69*(2), 223-224. doi:10.1212/01.wnl.0000271777.50910.73

Caminiti, S. P., Presotto, L., Baroncini, D., Garibotto, V., Moresco, R. M., Gianolli, L., . . . Perani, D. (2017). Axonal damage and loss of connectivity in nigrostriatal and mesolimbic dopamine pathways in early Parkinson's disease. *Neuroimage Clin, 14*(C), 734-740. doi:10.1016/j.nicl.2017.03.011

Cannon, J. R., & Greenamyre, J. T. (2012). Gene–environment interactions in Parkinson's disease: Specific evidence in humans and mammalian models. *Neurobiol Dis, 57*, 38-46. doi:10.1016/j.nbd.2012.06.025

Capriotti, T., & Terzakis, K. (2016). Parkinson Disease. *Home Healthc Now, 34*(6), 300-307. doi:10.1097/NHH.0000000000000398

Collier, T. J., Kanaan, N. M., & Kordower, J. H. (2011). Ageing as a primary risk factor for Parkinson's disease: evidence from studies of non-human primates. *Nat Rev Neurosci, 12*(6), 359-366. doi:10.1038/nrn3039

Cope, T. E., Baguley, D. M., & Griffiths, T. D. (2015). The functional anatomy of central auditory processing. *Pract Neurol, 15*(4), 302-308. doi:10.1136/practneurol-2014-001073

Crowley, E. K., Nolan, Y. M., & Sullivan, A. M. (2019). Exercise as a therapeutic intervention for motor and non-motor symptoms in Parkinson's disease: Evidence from rodent models. *Prog Neurobiol, 172*, 2-22. doi:10.1016/j.pneurobio.2018.11.003

Damsma, A., & van Rijn, H. (2017). Pupillary response indexes the metrical hierarchy of unattended rhythmic violations. *Brain Cogn, 111*, 95-103. doi:10.1016/j.bandc.2016.10.004

Darweesh, S. K. L., Koudstaal, P. J., Stricker, B. H., Hofman, A., & Ikram, M. A. (2016). Trends in the Incidence of Parkinson Disease in the General Population: The Rotterdam Study. *Am J Epidemiol, 183*(11), 1018-1026. doi:10.1093/aje/kwv271

Dawson, T. M., & Dawson, V. L. (2010). The role of parkin in familial and sporadic Parkinson's disease: The Role of Parkin in Familial and Sporadic PD. *Movement disorders, 25*(S1), S32-S39. doi:10.1002/mds.22798

de Zambotti, M., Trinder, J., Silvani, A., Colrain, I. M., & Baker, F. C. (2018). Dynamic coupling between the central and autonomic nervous systems during sleep: A review. *Neurosci Biobehav Rev, 90*, 84-103. doi:10.1016/j.neubiorev.2018.03.027

Del Tredici, K., & Braak, H. (2013). Dysfunction of the locus coeruleus–norepinephrine system and related circuitry in Parkinson's disease-related dementia. *J Neurol Neurosurg Psychiatry, 84*(7), 774-783. doi:10.1136/jnnp-2011-301817

Dick, F. D., De Palma, G., Ahmadi, A., Scott, N. W., Prescott, G. J., Bennett, J., . . . Felice, A. (2007). Environmental risk factors for Parkinson's disease and parkinsonism: the Geoparkinson study. *Occup Environ Med, 64*(10), 666-672. doi:10.1136/oem.2006.027003

Dorsey, E. R., Constantinescu, R., Thompson, J. P., Biglan, K. M., Holloway, R. G., Kieburtz, K., . . . Tanner, C. M. (2007). Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology, 68*(5), 384-386. doi:10.1212/01.wnl.0000247740.47667.03

Dorsey, E. R., Sherer, T., Okun, M. S., & Bloem, B. R. (2018). The emerging evidence of the Parkinson pandemic. *Journal of Parkinson's disease, 8*(s1), S3-S8.

Dowlati, E., Sarpong, K., Kamande, S., Carroll, A. H., Murray, J., Wiley, A., . . . Felbaum, D. R. (2021). Abnormal neurological pupil index is associated with malignant cerebral edema after mechanical thrombectomy in large vessel occlusion patients. *Neurol Sci*. doi:10.1007/s10072-021-05218-x

Drew, D. S., Muhammed, K., Baig, F., Kelly, M., Saleh, Y., Sarangmat, N., . . . Husain, M. (2020). Dopamine and reward hypersensitivity in Parkinson's disease with impulse control disorder. *Brain, 143*(8), 2502-2518. doi:10.1093/brain/awaa198

Dütsch, M., Marthol, H., Michelson, G., Neundörfer, B., & Hilz, M. J. (2004). Pupillography refines the diagnosis of diabetic autonomic neuropathy. *J Neurol Sci, 222*(1), 75-81. doi:10.1016/j.jns.2004.04.008

Einhäuser, W., Koch, C., & Carter, O. L. (2010). Pupil dilation betrays the timing of decisions. *Front Hum Neurosci, 4*, 18-18. doi:10.3389/fnhum.2010.00018

Fearnley, J. M., & Lees, A. J. (1991). Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain, 114*(5), 2283-2301.

Fellows, S. J., Noth, J., & Schwarz, M. (1998). Precision grip and Parkinson's disease. *Brain, 121*(9), 1771-1784. doi:10.1093/brain/121.9.1771

Fink, L. K., Hurley, B. K., Geng, J. J., & Janata, P. (2018). A linear oscillator model predicts dynamic temporal attention and pupillary entrainment to rhythmic patterns. *J Eye Mov Res, 11*(2). doi:10.16910/jemr.11.2.12

Fraser, J. A., Newman, N. J., & Biousse, V. (2011). Disorders of the optic tract, radiation, and occipital lobe. *Handb Clin Neurol, 102*, 205-221. doi:10.1016/B978-0-444-52903-9.00014-5

Freeman, W. D., & Vatz, K. A. (2010). The future of neurology. *Neurol Clin, 28*(2), 537-561. doi:10.1016/j.ncl.2009.11.006

Friedman, D., Hakerem, G., Sutton, S., & Fleiss, J. L. (1973). Effect of stimulus uncertainty on the pupillary dilation response and the vertex evoked potential. *Electroencephalogr Clin Neurophysiol, 34*(5), 475-484. doi:10.1016/0013-4694(73)90065-5

Færøvik, U., Specht, K., & Vikene, K. (2021). Suppression, Maintenance, and Surprise: Neuronal Correlates of Predictive Processing Specialization for Musical Rhythm. *Frontiers in neuroscience, 15*, 674050-674050. doi:10.3389/fnins.2021.674050

Garrido, M. I., Kilner, J. M., Stephan, K. E., & Friston, K. J. (2008). The mismatch negativity: A review of underlying mechanisms. *Clin Neurophysiol, 120*(3), 453-463. doi:10.1016/j.clinph.2008.11.029

Geiser, E., Ziegler, E., Jancke, L., & Meyer, M. (2009). Early electrophysiological correlates of meter and rhythm processing in music perception. *Cortex, 45*(1), 93-102. doi:10.1016/j.cortex.2007.09.010

Giladi, N., McDermott, M. P., Fahn, S., Przedborski, S., Jankovic, J., Stern, M., & Tanner, C. (2001). Freezing of gait in PD - Prospective assessment in the DATATOP cohort. *Neurology, 56*(12), 1712-1721. doi:10.1212/WNL.56.12.1712

Giza, E., Fotiou, D., Bostantjopoulou, S., Katsarou, Z., & Karlovasitou, A. (2011). Pupil Light Reflex in Parkinson's Disease: Evaluation With Pupillometry. *International journal of neuroscience, 121*(1), 37-43. doi:10.3109/00207454.2010.526730

Granholm, E., Asarnow, R. F., Sarkin, A. J., & Dykes, K. L. (1996). Pupillary responses index cognitive resource limitations. *Psychophysiology, 33*(4), 457-461. doi:10.1111/j.1469-8986.1996.tb01071.x

Grenzebach, J., Wegner, T. G. G., Einhäuser, W., & Bendixen, A. (2021). Pupillometry in auditory multistability. *PloS one, 16*(6), e0252370-e0252370. doi:10.1371/journal.pone.0252370

Griffiths, H. R., Møller, L., Bartosz, G., Bast, A., Bertoni-Freddari, C., Collins, A., . . . Astley, S. B. (2002). Biomarkers. *Mol Aspects Med, 23*(1), 101-208. doi:10.1016/S0098-2997(02)00017-1

Guo, T., Wu, J., Zhou, C., Guan, X., Gao, T., Bai, X., . . . Zhang, M. (2020). Aberrant Fiber Coherence of Amygdala−Accumbens−Pallidum Pathway Is Associated With Disorganized Nigrostriatal−Nigropallidal Pathway in Parkinson's Disease. *J Magn Reson Imaging, 52*(6), 1799-1808. doi:10.1002/jmri.27273

Gupta, M., & Bordoni, B. (2020). Neuroanatomy, Visual Pathway. In *StatPearls [Internet]*: StatPearls Publishing.

Haslinger, B., Erhard, P., Kämpfe, N., Boecker, H., Rummeny, E., Schwaiger, M., . . . Ceballos-Baumann, A. O. (2001). Event-related functional magnetic resonance imaging in Parkinson's disease before and after levodopa. *Brain, 124*(3), 558-570. doi:10.1093/brain/124.3.558

Hawkes, C. H. (2008). The prodromal phase of sporadic Parkinson's disease: Does it exist and if so how long is it? *Mov. Disord, 23*(13), 1799-1807. doi:10.1002/mds.22242

Ho, A. K., Iansek, R., Marigliani, C., Bradshaw, J. L., & Gates, S. (1998). Speech impairment in a large sample of patients with Parkinson's disease. *Behav Neurol, 11*(3), 131-137. doi:10.1155/1999/327643

Hodge, C. F. (1894). Changes in ganglion cells from birth to senile death. Observations on man and honey-bee. *The Journal of physiology, 17*(1-2), 128.121.

Homayoun, H. (2018). Parkinson Disease. *Ann Intern Med, 169*(5), ITC33-ITC48. doi:10.7326/AITC201809040

Horsfall, L., Petersen, I., Walters, K., & Schrag, A. (2013). Time trends in incidence of Parkinson's disease diagnosis in UK primary care. *J Neurol, 260*(5), 1351-1357. doi:10.1007/s00415-012-6804-z

Huron, D. (2008). *Sweet anticipation: Music and the psychology of expectation*: MIT press.

Höfle, M., Kenntner-Mabiala, R., Pauli, P., & Alpers, G. W. (2008). You can see pain in the eye: Pupillometry as an index of pain intensity under different luminance conditions. *Int J Psychophysiol, 70*(3), 171-175. doi:10.1016/j.ijpsycho.2008.06.008

Jain, S. (2010). Multi-organ autonomic dysfunction in Parkinson disease. *Parkinsonism Relat Disord, 17*(2), 77-83. doi:10.1016/j.parkreldis.2010.08.022

Janata, P., Tomic, S. T., & Haberman, J. M. (2012). Sensorimotor Coupling in Music and the Psychology of the Groove. *J Exp Psychol Gen, 141*(1), 54-75. doi:10.1037/a0024208

Johansson, R. S., & Westling, G. (1984). Roles of glabrous skin receptors and sensorimotor memory in automatic control of precision grip when lifting rougher or more slippery objects. *Exp Brain Res, 56*(3), 550-564. doi:10.1007/BF00237997

Kahneman, D., & Beatty, J. (1966). Pupil Diameter and Load on Memory. *Science, 154*(3756), 1583-1585. doi:10.1126/science.154.3756.1583

Kidd, D. (2014). The optic chiasm. *Clin. Anat, 27*(8), 1149-1158. doi:10.1002/ca.22385

Kinner, V. L., Kuchinke, L., Dierolf, A. M., Merz, C. J., Otto, T., & Wolf, O. T. (2017). What our eyes tell us about feelings: Tracking pupillary responses during emotion regulation processes: Pupillary responses during emotion regulation. *Psychophysiology, 54*(4), 508-518. doi:10.1111/psyp.12816

Klein, C., & Westenberger, A. (2012). Genetics of Parkinson's disease. *Cold Spring Harb Perspect Med, 2*(1), a008888-a008888. doi:10.1101/cshperspect.a008888

Kline, J. E., Huang, H. J., Snyder, K. L., & Ferris, D. P. (2015). Isolating gait-related movement artifacts in electroencephalography during human walking. *J. Neural Eng, 12*(4), 046022-046022. doi:10.1088/1741-2560/12/4/046022

Koelsch, S., Busch, T., Jentschke, S., & Rohrmeier, M. (2016). Under the hood of statistical learning: A statistical MMN reflects the magnitude of transitional probabilities in auditory sequences. *Sci Rep, 6*(1), 19741-19741. doi:10.1038/srep19741

Ladinig, O., Honing, H., Háden, G., & Winkler, I. (2009). Probing Attentive and Preattentive Emergent Meter in Adult Listeners without Extensive Music Training. *Music perception, 26*(4), 377-386. doi:10.1525/mp.2009.26.4.377

Laeng, B., Sirois, S., & Gredebäck, G. (2012). Pupillometry: A Window to the Preconscious? *Perspect Psychol Sci, 7*(1), 18-27. doi:10.1177/1745691611427305

Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functional neuroanatomy of the basal ganglia. *Cold Spring Harbor perspectives in medicine, 2*(12), a009621.

Lehmann, S. J., & Corneil, B. D. (2016). Transient Pupil Dilation after Subsaccadic Microstimulation of Primate Frontal Eye Fields. *J Neurosci, 36*(13), 3765-3776. doi:10.1523/JNEUROSCI.4264-15.2016

Letanneux, A., Danna, J., Velay, J.-L., Viallet, F., & Pinto, S. (2014). From micrographia to Parkinson's disease dysgraphia. *Mov Disord, 29*(12), 1467-1475. doi:10.1002/mds.25990

Lewis, G. A., & Bidelman, G. M. (2019). Autonomic Nervous System Correlates of Speech Categorization Revealed Through Pupillometry. *Front Neurosci, 13*, 1418-1418. doi:10.3389/fnins.2019.01418

Liao, H.-I., Kidani, S., Yoneya, M., Kashino, M., & Furukawa, S. (2016). Correspondences among pupillary dilation response, subjective salience of sounds, and loudness. *Psychon Bull Rev, 23*(2), 412-425. doi:10.3758/s13423-015-0898-0

Lim, S.-Y., & Lang, A. E. (2010). The nonmotor symptoms of Parkinson's disease-An overview. *Mov. Disord, 25*(S1), S123-S130. doi:10.1002/mds.22786

Lin, H., Saunders, B., Hutcherson, C. A., & Inzlicht, M. (2018). Midfrontal theta and pupil dilation parametrically track subjective conflict (but also surprise) during intertemporal choice. *Neuroimage, 172*, 838-852. doi:10.1016/j.neuroimage.2017.10.055

Lionnet, A., Leclair-Visonneau, L., Neunlist, M., Murayama, S., Takao, M., Adler, C. H., . . . Beach, T. G. (2018). Does Parkinson's disease start in the gut? *Acta Neuropathol, 135*(1), 1-12. doi:10.1007/s00401-017-1777-8

London, A., Benhar, I., & Schwartz, M. (2013). The retina as a window to the brain-from eye research to CNS disorders. *Nat Rev Neurol, 9*(1), 44-53. doi:10.1038/nrneurol.2012.227

Lussier, B. L., Olson, D. M., & Aiyagari, V. (2019). Automated Pupillometry in Neurocritical Care: Research and Practice. *Curr Neurol Neurosci Rep, 19*(10), 1-11. doi:10.1007/s11910-019-0994-z

Magnotti, J. F., Dzeda, K. B., Wegner-Clemens, K., Rennig, J., & Beauchamp, M. S. (2020). Weak observer–level correlation and strong stimulus-level correlation between the McGurk effect and audiovisual speech-in-noise: A causal inference explanation. *Cortex, 133*, 371-383. doi:10.1016/j.cortex.2020.10.002

Marois, A., & Vachon, F. (2018). Can pupillometry index auditory attentional capture in contexts of active visual processing? *Journal of cognitive psychology (Hove, England), 30*(4), 484-502. doi:10.1080/20445911.2018.1470518

Martinez-Martin, P., Rodriguez-Blazquez, C., Kurtis, M. M., & Chaudhuri, K. R. (2011). The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov. Disord, 26*(3), 399-406. doi:10.1002/mds.23462

Matouskova, O., Slanar, O., Chytil, L., & Perlik, F. (2011). Pupillometry in healthy volunteers as a biomarker of tramadol efficacy: Pupillometry as a measure of tramadol efficacy. *Journal of clinical pharmacy and therapeutics, 36*(4), 513-517. doi:10.1111/j.1365-2710.2010.01203.x

McAnany, J. J., Smith, B. M., Garland, A., & Kagen, S. L. (2018). iPhone-based Pupillometry: A Novel Approach for Assessing the Pupillary Light Reflex. *Optom Vis Sci, 95*(10), 953-958. doi:10.1097/OPX.0000000000001289

McDougal, D. H., & Gamlin, P. D. (2015). Autonomic control of the eye. *Comprehensive Physiology, 5*(1), 439.

McGregor, M. M., & Nelson, A. B. (2019). Circuit Mechanisms of Parkinson's Disease. *Neuron, 101*(6), 1042-1056. doi:10.1016/j.neuron.2019.03.004

McGurk, H., & Macdonald, J. (1976). Hearing lips and seeing voices. *Nature, 264*(5588), 746-748. doi:10.1038/264746a0

McLaren, J. W., Hauri, P. J., Lin, S.-C., & Harris, C. D. (2002). Pupillometry in clinically sleepy patients. *Sleep Med, 3*(4), 347-352. doi:10.1016/S1389-9457(02)00017-5

Mill, R. D., O'Connor, A. R., & Dobbins, I. G. (2016). Pupil dilation during recognition memory: Isolating unexpected recognition from judgment uncertainty. *Cognition, 154*, 81-94. doi:10.1016/j.cognition.2016.05.018

Montes-Lourido, P., Kar, M., Kumbam, I., & Sadagopan, S. (2021). Pupillometry as a reliable metric of auditory detection and discrimination across diverse stimulus paradigms in animal models. *Sci Rep, 11*(1), 3108-3108. doi:10.1038/s41598-021-82340-y

Morens, D. M., Davis, J. W., Grandinetti, A., Ross, G. W., Popper, J. S., & White, L. R. (1996). Epidemiologic observations on Parkinson's disease: Incidence and mortality in a prospective study of middle-aged men. *Neurology, 46*(4), 1044-1050. doi:10.1212/WNL.46.4.1044

Morris, I. B., Vasudevan, E., Schedel, M., Weymouth, D., Loomis, J., Pinkhasov, T., & Muratori, L. M. (2019). Music to One's Ears: Familiarity and Music Engagement in People With Parkinson's Disease. *Front Neurosci, 13*, 661-661. doi:10.3389/fnins.2019.00661

Moustafa, A. A., Chakravarthy, S., Phillips, J. R., Gupta, A., Keri, S., Polner, B., . . . Jahanshahi, M. (2016). Motor symptoms in Parkinson's disease: A unified framework. *Neurosci Biobehav Rev, 68*, 727-740. doi:10.1016/j.neubiorev.2016.07.010

Nandipati, S., & Litvan, I. (2016). Environmental Exposures and Parkinson's Disease. *Int J Environ Res Public Health, 13*(9), 881. doi:10.3390/ijerph13090881

Napier, J. R. (1956). The prehensile movements of the human hand. *J Bone Joint Surg Br, 38-B*(4), 902-913. doi:10.1302/0301-620X.38B4.902

Neuhuber, W., & Schrödl, F. (2010). Autonomic control of the eye and the iris. *Auton Neurosci, 165*(1), 67-79. doi:10.1016/j.autneu.2010.10.004

O'Regan, S., Faul, S., & Marnane, W. (2012). Automatic detection of EEG artefacts arising from head movements using EEG and gyroscope signals. *Med Eng Phys, 35*(7), 867-874. doi:10.1016/j.medengphy.2012.08.017

Ohlenforst, B., Zekveld, A. A., Lunner, T., Wendt, D., Naylor, G., Wang, Y., . . . Kramer, S. E. (2017). Impact of stimulus-related factors and hearing impairment on listening effort as indicated by pupil dilation. *Hear Res, 351*, 68-79. doi:10.1016/j.heares.2017.05.012

Oliva, M., & Anikin, A. (2018). Pupil dilation reflects the time course of emotion recognition in human vocalizations. *Sci Rep, 8*(1), 4871-4810. doi:10.1038/s41598-018-23265-x

Ortuño-Lizarán, I., Sánchez-Sáez, X., Lax, P., Serrano, G. E., Beach, T. G., Adler, C. H., & Cuenca, N. (2020). Dopaminergic Retinal Cell Loss and Visual Dysfunction in Parkinson Disease. *Ann Neurol, 88*(5), 893-906. doi:10.1002/ana.25897

Ouchi, Y., Kanno, T., Okada, H., Yoshikawa, E., Futatsubashi, M., Nobezawa, S., . . . Tanaka, K. (2001). Changes in dopamine availability in the nigrostriatal and mesocortical dopaminergic systems by gait in Parkinson's disease. *Brain, 124*(4), 784-792. doi:10.1093/brain/124.4.784

Park, H. K., Yoo, J. Y., Kwon, M., Lee, J.-H., Lee, S. J., Kim, S. R., . . . Chung, S. J. (2014). Gait freezing and speech disturbance in Parkinson's disease. *Neurol Sci, 35*(3), 357-363. doi:10.1007/s10072-013-1519-1

Parkinson, J. (2002). An essay on the shaking palsy. *The Journal of neuropsychiatry and clinical neurosciences, 14*(2), 223-236.

Perkins, J. E., Janzen, A., Bernhard, F. P., Wilhelm, K., Brien, D. C., Huang, J., . . . Oertel, W. H. (2021). Saccade, Pupil, and Blink Responses in Rapid Eye Movement Sleep Behavior Disorder. *Mov Disord, 36*(7), 1720-1726. doi:10.1002/mds.28585

Peterson, D. C., & Hamel, R. (2018). Neuroanatomy, auditory pathway.

Phillips, J. G., Bradshaw, J. L., Iansek, R., & Chiu, E. (1993). MOTOR FUNCTIONS OF THE BASAL GANGLIA. *Psychol Res, 55*(2), 175-181. doi:10.1007/BF00419650

Polito, L., Greco, A., & Seripa, D. (2016). Genetic Profile, Environmental Exposure, and Their Interaction in Parkinson's Disease. *Parkinsons Dis, 2016*, 6465793-6465799. doi:10.1155/2016/6465793

Prensa, L., Giménez-Amaya, J. M., Parent, A., Bernácer, J., & Cebrián, C. (2009). The Nigrostriatal Pathway: Axonal Collateralization and Compartmental Specificity. *Birth,*

Life and Death of Dopaminergic Neurons in the Substantia Nigra, 49-58. doi:10.1007/978-3-211-92660-4_4

Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. L. (2014). The prevalence of Parkinson's disease: A systematic review and meta-analysis. *Mov Disord, 29*(13), 1583-1590. doi:10.1002/mds.25945

Purves, D., & Brannon, E. M. (2013). *Principles of cognitive neuroscience* (2nd ed. ed.). Sunderland, Mass: Sinauer Associates.

Rees, R. N., Acharya, A. P., Schrag, A., & Noyce, A. J. (2018). An early diagnosis is not the same as a timely diagnosis of Parkinson's disease. *F1000Res, 7*, 1106. doi:10.12688/f1000research.14528.1

Remington, L. A., & Goodwin, D. (2011). *Clinical anatomy of the visual system E-Book*: Elsevier Health Sciences.

Ring, H. A., & Serra-Mestres, J. (2002). Neuropsychiatry of the basal ganglia. *J Neurol Neurosurg Psychiatry, 72*(1), 12-21. doi:10.1136/jnnp.72.1.12

Rizzo, G., Copetti, M., Arcuti, S., Martino, D., Fontana, A., & Logroscino, G. (2016). Accuracy of clinical diagnosis of Parkinson disease: A systematic review and meta-analysis. *Neurology, 86*(6), 566-576. doi:10.1212/WNL.0000000000002350

Robbins, J. A., Logemann, J. A., & Kirshner, H. S. (1986). Swallowing and speech production in Parkinson's disease. *Ann Neurol, 19*(3), 283-287. doi:10.1002/ana.410190310

Rosenblum, S., Samuel, M., Zlotnik, S., Erikh, I., & Schlesinger, I. (2013). Handwriting as an objective tool for Parkinson's disease diagnosis. *J Neurol, 260*(9), 2357-2361. doi:10.1007/s00415-013-6996-x

Ross, C. A., & Smith, W. W. (2007). Gene–environment interactions in Parkinson's disease. *Parkinsonism Relat Disord, 13*, S309-S315. doi:10.1016/S1353-8020(08)70022-1

Sabatini, U., Boulanouar, K., Fabre, N., Martin, F., Carel, C., Colonnese, C., . . . Rascol, O. (2000). Cortical motor reorganization in akinetic patients with Parkinson's disease - A functional MRI study. *Brain, 123*, 394-403. doi:10.1093/brain/123.2.394

Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nat Rev Neurosci, 10*(3), 211-223. doi:10.1038/nrn2573

Savica, R., Grossardt, B. R., Bower, J. H., Ahlskog, J. E., & Rocca, W. A. (2016). Time Trends in the Incidence of Parkinson Disease. *JAMA Neurol, 73*(8), 981-989. doi:10.1001/jamaneurol.2016.0947

Schapira, A. H. V., Chaudhuri, K. R., & Jenner, P. (2017). Non-motor features of Parkinson disease. *Nat Rev Neurosci, 18*(7), 435-450. doi:10.1038/nrn.2017.62

Schneider, C. B., Ziemssen, T., Schuster, B., Seo, H.-S., Haehner, A., & Hummel, T. (2009). Pupillary responses to intranasal trigeminal and olfactory stimulation. *J Neural Transm (Vienna), 116*(7), 885-889. doi:10.1007/s00702-009-0244-7

Seiss, E., & Praamstra, P. (2004). The basal ganglia and inhibitory mechanisms in response selection: evidence from subliminal priming of motor responses in Parkinson's disease. *Brain, 127*(2), 330-339. doi:10.1093/brain/awh043

Seppi, K., Ray Chaudhuri, K., Coelho, M., Fox, S. H., Katzenschlager, R., Perez Lloret, S., . . . Djamshidian-Tehrani, A. (2019). Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. *Mov Disord, 34*(2), 180-198. doi:10.1002/mds.27602

Sirois, S., & Brisson, J. (2014). Pupillometry. *WIREs Cogn Sci, 5*(6), 679-692. doi:10.1002/wcs.1323 This article is categorized under: Psychology > Attention Psychology > Perception and Psychophysics Psychology > Theory and Methods
10.1002/wcs.1323

Soeken, T. A., Alonso, A., Grant, A., Calvillo, E., Gutierrez-Flores, B., Clark, J., . . . Bershad, E. M. (2018). Quantitative Pupillometry for Detection of Intracranial Pressure Changes During Head-Down Tilt. *Aerosp Med Hum Perform, 89*(8), 717-723. doi:10.3357/AMHP.4929.2018

Spector, R. H. (1990). The pupils. *Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition*.

Steinhauer, S., & Zubin, J. (1982). Vulnerability to schizophrenia: Information processing in the pupil and event-related potential. In *Biological markers in psychiatry and neurology* (pp. 371-385): Elsevier.

Stergiou, V., Fotiou, D., Tsiptsios, D., Haidich, B., Nakou, M., Giantselidis, C., & Karlovasitou, A. (2009). Pupillometric findings in patients with Parkinson's disease and cognitive disorder. *Int J Psychophysiol, 72*(2), 97-101. doi:10.1016/j.ijpsycho.2008.10.010

Stergiou, V., Lithari, C., Zafeiridou, G., Nakou, M., Tychalas, A., & Karvolasitou, A. (2010). Pupillometry in Parkinson's disease and coexisting cognitive disorder. *International journal of psychophysiology, 77*(3), 264-264. doi:10.1016/j.ijpsycho.2010.06.095

Struzyna, L. A., Browne, K. D., Brodnik, Z. D., Burrell, J. C., Harris, J. P., Chen, H. I., . . . Cullen, D. K. (2018). Tissue engineered nigrostriatal pathway for treatment of Parkinson's disease. *J Tissue Eng Regen Med, 12*(7), 1702-1716. doi:10.1002/term.2698

Tantiwongkosi, B., & Hesselink, J. R. (2015). Imaging of Ocular Motor Pathway. *Neuroimaging Clin N Am, 25*(3), 425-438. doi:10.1016/j.nic.2015.05.006

Tassorelli, C., Micieli, G., Osipova, Marcheselli, S., Rossi, F., & Nappi, G. (1998). Combined evaluation of pupillary and cardiovascular responses to cold pressor test in cluster headache patients. *Cephalalgia, 18*(10), 668-674. doi:10.1046/j.1468-2982.1998.1810668.x

Taylor, W. R., Chen, J. W., Meltzer, H., Gennarelli, T. A., Kelbch, C., Knowlton, S., . . . Marshall, L. F. (2003). Quantitative pupillometry, a new technology: normative data and preliminary observations in patients with acute head injury - Technical note. *J Neurosurg, 98*(1), 205-213. doi:10.3171/jns.2003.98.1.0205

Teulings, H.-L., & Stelmach, G. E. (1991). Control of stroke size, peak acceleration, and stroke duration in Parkinsonian handwriting. *Human movement science, 10*(2), 315-334. doi:10.1016/0167-9457(91)90010-U

Teulings, H. L., Contreras-Vidal, J. L., Stelmach, G. E., & Adler, C. H. (2002). Adaptation of handwriting size under distorted visual feedback in patients with Parkinson's disease and elderly and young controls. *J Neurol Neurosurg Psychiatry, 72*(3), 315-324. doi:10.1136/jnnp.72.3.315

Turnbull, P. R. K., Irani, N., Lim, N., & Phillips, J. R. (2017). Origins of Pupillary Hippus in the Autonomic Nervous System. *Invest Ophthalmol Vis Sci, 58*(1), 197-203. doi:10.1167/iovs.16-20785

van Hooijdonk, R., Mathot, S., Schat, E., Spencer, H., van der Stigchel, S., & Dijkerman, H. C. (2019). Touch-induced pupil size reflects stimulus intensity, not subjective pleasantness. *Exp Brain Res, 237*(1), 201-210. doi:10.1007/s00221-018-5404-2

Vikene, K., Skeie, G. O., & Specht, K. (2018). Abnormal phasic activity in saliency network, motor areas, and basal ganglia in Parkinson's disease during rhythm perception. *Hum Brain Mapp, 40*(3), 916-927. doi:10.1002/hbm.24421

Vikene, K., Skeie, G. O., & Specht, K. (2019). Compensatory task-specific hypersensitivity in bilateral planum temporale and right superior temporal gyrus during auditory rhythm and omission processing in Parkinson's disease. *Sci Rep, 9*(1), 12623-12629. doi:10.1038/s41598-019-48791-0

Vogelzang, M., Hendriks, P., & van Rijn, H. (2016). Pupillary responses reflect ambiguity resolution in pronoun processing. *Language, cognition and neuroscience, 31*(7), 876-885. doi:10.1080/23273798.2016.1155718

Vuust, P., Gebauer, L. K., & Witek, M. A. G. (2014). Neural Underpinnings of Music: The Polyrhythmic Brain. *Adv Exp Med Biol, 829*, 339-356. doi:10.1007/978-1-4939-1782-2_18

Walter, H., Lesch, O. M., Stohr, H., Grunberger, J., & Gutierrez-Lobos, K. (2006). Reaction to pain stimulus before and during hypnosis measured by pupillary reaction. *Am J Clin Hypn, 48*(2-3), 145-152.

Wang, C.-A., McInnis, H., Brien, D. C., Pari, G., & Munoz, D. P. (2016). Disruption of pupil size modulation correlates with voluntary motor preparation deficits in Parkinson's disease. *Neuropsychologia, 80*, 176-184. doi:10.1016/j.neuropsychologia.2015.11.019

Weiner, R. I., & Ganong, W. F. (1978). Role of brain monoamines and histamine in regulation of anterior pituitary secretion. *Physiol Rev, 58*(4), 905-976. doi:10.1152/physrev.1978.58.4.905

Wilkinson, M. J. (2018). Anatomy of the human orbit. *Operative techniques in otolaryngology--head and neck surgery, 29*(4), 186-192. doi:10.1016/j.otot.2018.10.002

Willing, J., & Wagner, C. K. (2016). Progesterone Receptor Expression in the Developing Mesocortical Dopamine Pathway: Importance for Complex Cognitive Behavior in Adulthood. *Neuroendocrinology, 103*(3-4), 207-222. doi:10.1159/000434725

Wolff, M. J., Scholz, S., Akyürek, E. G., & van Rijn, H. (2015). Two visual targets for the price of one?: Pupil dilation shows reduced mental effort through temporal integration. *Psychon Bull Rev, 22*(1), 251-257. doi:10.3758/s13423-014-0667-5

Wu, S. Z., Masurkar, A. V., & Balcer, L. J. (2020). Afferent and Efferent Visual Markers of Alzheimer's Disease: A Review and Update in Early Stage Disease. *Front Aging Neurosci, 12*, 572337-572337. doi:10.3389/fnagi.2020.572337

Wu, T., & Hallett, M. (2005). A functional MRI study of automatic movements in patients with Parkinson's disease. *Brain, 128*(10), 2250-2259. doi:10.1093/brain/awh569

Yu, H., Sternad, D., Corcos, D. M., & Vaillancourt, D. E. (2007). Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *Neuroimage, 35*(1), 222-233. doi:10.1016/j.neuroimage.2006.11.047

Zekveld, A. A., Koelewijn, T., & Kramer, S. E. (2018). The pupil dilation response to auditory stimuli: current state of knowledge. *Trends in hearing, 22*, 2331216518777174.

Zhai, S., Shen, W., Graves, S. M., & Surmeier, D. J. (2019). Dopaminergic modulation of striatal function and Parkinson's disease. *J Neural Transm (Vienna), 126*(4), 411-422. doi:10.1007/s00702-019-01997-y

Zhai, S., Tanimura, A., Graves, S. M., Shen, W., & Surmeier, D. J. (2018). Striatal synapses, circuits, and Parkinson's disease. *Curr Opin Neurobiol, 48*, 9-16. doi:10.1016/j.conb.2017.08.004

Zhang, Y., Wu, I. W., Buckley, S., Coffey, C. S., Foster, E., Mendick, S., . . . Schuff, N. (2015). Diffusion tensor imaging of the nigrostriatal fibers in Parkinson's disease. *Mov Disord, 30*(9), 1229-1236. doi:10.1002/mds.26251

Zhao, T. C., Lam, H. T. G., Sohi, H., & Kuhl, P. K. (2017). Neural processing of musical meter in musicians and non-musicians. *Neuropsychologia, 106*, 289-297. doi:10.1016/j.neuropsychologia.2017.10.007